

COPPER-CATALYZED ARYLATIONS AND HETEROARYLATIONS

DOI: <http://dx.medra.org/10.17374/targets.2023.26.249>Muhammad Bilal,^a Moniba Sharif,^b Nasir Rasool,^{*b} Iram Kanwal,^b Gulraiz Ahmad,^b Peter Langer^{*c,d}^aSchool of Chemistry and Chemical Engineering, Shandong University, Jinan 250100, China^bDepartment of Chemistry, Government College, University Faisalabad, 38000, Pakistan^cInstitut für Chemie, Universität Rostock, Albert-Einstein-Str. 3a, 18059 Rostock, Germany^dLeibniz-Institut für Katalyse, Universität Rostock e.V., Albert-Einstein-Str. 29a, 18059 Rostock, Germany(e-mail: nasirrasool@gcuf.edu.pk, peter.langer@uni-rostock.de)

Abstract. One of the most important challenges in organic synthesis is the field of cross-coupling reactions that provide carbon-carbon and carbon-heteroatom bonds. Copper-catalyzed cross-coupling reactions are well known reactions in organic synthesis and play a key role in arylation and heteroarylation reactions via C–C, C–N, C–O, and C–S cross-coupling reactions. These reactions are used to synthesize heterocycles, biologically active compounds and natural products. This review covers recent developments in copper-catalyzed arylations and heteroarylations by cross-coupling reactions achieved in the last two decades with special emphasis on substrates, different catalysts and reaction conditions.

Contents

1. Introduction
2. C–N cross-coupling
 - 2.1. Copper halides
 - 2.2. Copper acetate
 - 2.3. Copper triflate
 - 2.4. Copper sulphate
 - 2.5. Copper oxide
 - 2.6. Copper MOF
3. C–O cross-coupling
 - 3.1. Copper halides
 - 3.2. Copper acetate
4. C–S cross-coupling
 - 4.1. Copper halide
 - 4.2. Copper acetate
 - 4.3. Copper triflate
 - 4.4. Copper oxide
5. Conclusions
- Acknowledgement
- References

1. Introduction

Copper (Cu) is the first metal used to catalyze the formation of carbon–carbon and carbon–heteroatom bonds. Cross-coupling reaction between organic electron-deficient species (electrophiles) and various organometallic reagents resulted in various important bonds, such as, C–P, C–S, C–O, C–H, C–N, and C–S. These are formed in the presence of transition metals, particularly palladium and nickel.¹ Palladium is a rather expensive metal that has been traditionally used in many cross-coupling reactions as catalyst. For economical reasons, it would be interesting to replace palladium and other expensive metals with less costly metals, such as copper.² Copper is a readily available metal and represents an environmentally friendly catalyst.³ In comparison to palladium, copper-catalyzed reactions frequently suffer from a lower tolerance to functional groups.⁴ Moreover, the stability of starting materials and products might be a problem, due to the required harsh reaction conditions.⁵

The cross-coupled products are often medicinally active and, thus, copper-based catalysts are a topic of interest for the synthesis of such compounds in an industrial environment.⁶ As a result of the C–O, C–S, and C–N cross-coupling reactions, various heterocycles can be formed which are also present in naturally occurring compounds. Heterocycles are present in many medicines and are important for drug discovery and

synthetic products.⁷

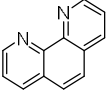

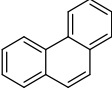

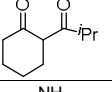

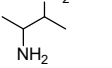
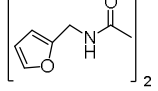
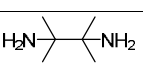

Copper-based complexes, such as Cu(OTf)₂, CuOAc, [Cu(OH)TMEDA]₂Cl₂, Copper(I) 2-thiophenecarboxylate (CuTc) and Cu halides are efficiently employed as catalysts for cross-coupling reactions. Various important cross-coupling reactions, such as the Chan-Lam cross-coupling, Sonogashira and Biginelli reactions as well as Ullmann type reactions are efficiently catalyzed by copper metal.^{2b,6a,8} The C–N, C–O and C–S cross-coupled products obtained have been reported to be pharmaceutically active or to be employed in agriculture.^{3a,7f,9}

This review covers the cross-coupling reactions of carbon with carbon, oxygen, nitrogen and sulphur in the presence of the inexpensive and readily available transition metal copper. Various copper-based complexes, such as copper acetate, copper triflates and a variety of copper halides are being used in this context.

2. C–N cross-coupling

The C–N cross-coupling reactions are catalyzed by using a low-cost, easily available Cu catalyst that is both economically and industrially beneficial. *N*-Heterocycles, bioactive compounds, and natural products all include the C–N moiety. *N*-Arylated pyrroles were formed as a result of the C–N cross-coupling reaction,¹⁰ of which are components of pharmaceutically active drugs. These chemicals have anti-cancer, anti-inflammatory, anti-HIV, and immunosuppressive properties.¹¹ The C–N cross-coupling in Ullmann-type reaction in the presence of Cu catalysts which are employed as precursors of *N*-heterocyclic carbenes (NHCs) in life science industries.¹² The ligands which are used in C–N cross-coupling are listed in Table 1.

Table 1. List of ligands used in C–N cross-coupling.

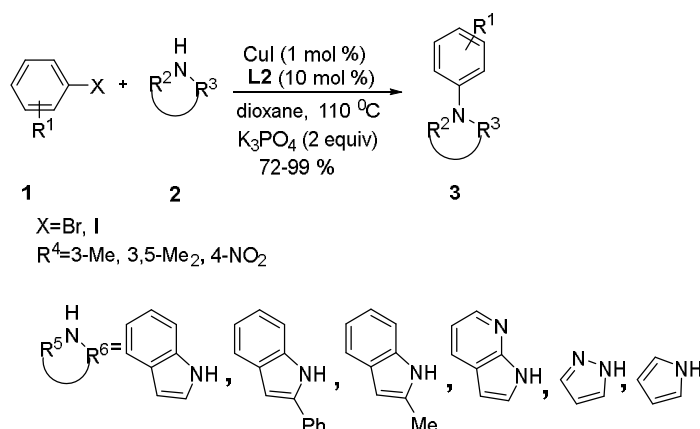
L1	1,10-Phenanthroline		L6	(1 <i>S</i> ,2 <i>S</i>)- <i>N,N'</i> -Dimethyl-cyclohexane-1,2-diamine	
L2	Phenanthrene		L7	Hexamethylphosphorotriamide (HMPT)	
L3	2-Isobutyrylcyclohexan-1-one		L8	Hexamethylenetetramine (HMTA)	
L4	Dimethylethylenediamine (DMEDA)		L9	<i>N,N'</i> -Bis((2-furyl)methyl)oxal-amide (BFMO)	
L5	Tetramethylethylenediamine (TMEDA)		L10	(1 <i>R</i> ,2 <i>R</i>)-1,2-Diaminocyclohexane	

2.1. Copper halides

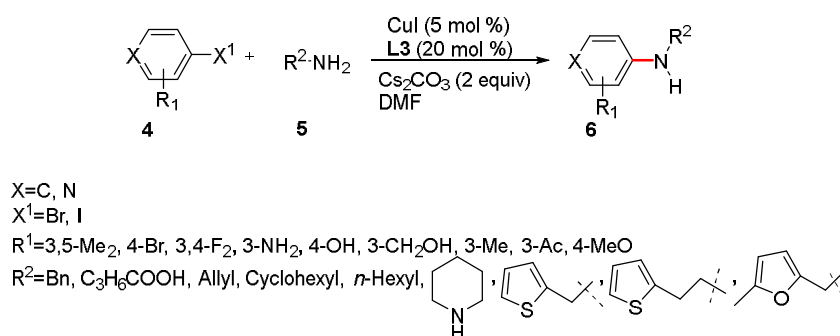
Amination reactions catalyzed by palladium are difficult to occur in the presence of certain functional groups such as primary and secondary amides as well as an aromatic ring having free NH or OH moieties that also contains sulfonate or halide groups.¹³ However, heterocycles were *N*-arylated and heterocyclic halides were aminated to a limited extent.¹⁴ Imidazoles were *N*-arylated in the presence of an additive such as 1,10-phenanthroline in the Ullmann reaction.¹⁵ Herein, aryl halides **1** reacted with various indoles/heterocycles **2** by employing CuI as catalyst, K₃PO₄ as base, dioxane solvent and ligand **L2** to afford maximum yields of arylated *N*-heterocycles **3** (Scheme 1). Various heterocycles such as 7-azaindole, phthalazinone, indoles, and pyrazoles were aminated in excellent yields by the above-mentioned methodology.¹⁶

A range of aryl/heteroaryl halides **4** was allowed to react in the presence of CuI as catalyst, 2-isobutyrylcyclohexanone as ligand **L3**, Cs₂CO₃ as base, and DMF as solvent with cyclic/acyclic amines **5**

at room temperature to produce good yields of *N*-arylated amines **6** (Scheme 2). Moreover, indole was generated quickly as a result of the intramolecular reaction of 2-bromophenethyl amine. At high temperatures, aryl bromides show the highest yields while the aryl iodides showed a lesser amount of product with electron-rich substituents and the reaction was unaffected by steric effects.¹⁷

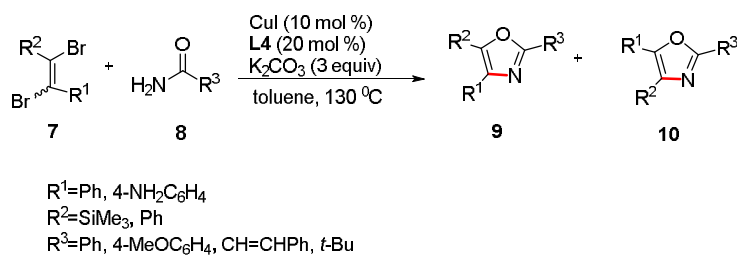


Scheme 1. Copper(I) iodide based C–N cross-coupling of aryl halides and various heterocycles.



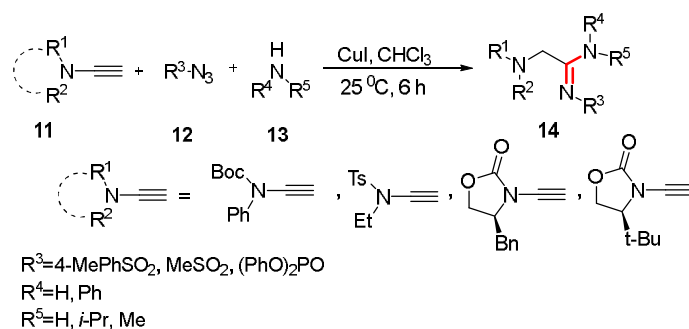
Scheme 2. C–N Cross-coupling reaction between aryl/heteroaryl halides and cyclic/acyclic amines.

In 2007, Schuh and colleagues synthesized substituted oxazoles **9** and **10** by the reaction of various primary amides **8** were regioselectively reacted with 1,2-dibromo alkenes **7** using CuI as catalyst, 1,2-dimethylethylenediamine (DMEDA) **L4** as ligand, K₂CO₃ as base, and toluene as solvent (Scheme 3). This reaction has a limitation that there was no product formed with olefins having a hydroxyl group. A wide range of functional groups, including amines, silyl, and methoxy were tolerated.¹⁸



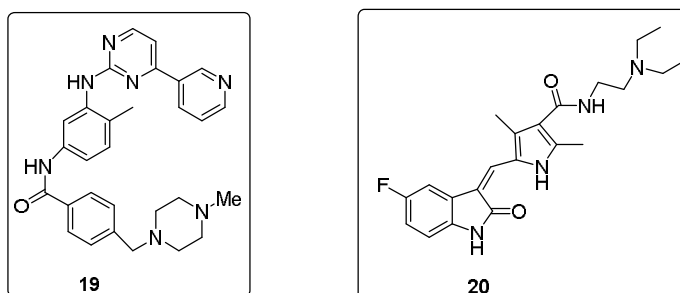
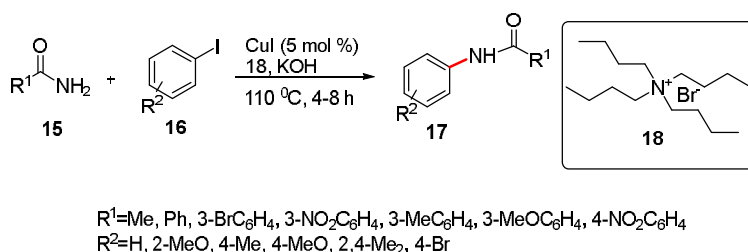
Scheme 3. Synthesis of substituted oxazoles using copper(I) iodide as catalyst.

Furthermore, the synthesis of aminoamidines **14** was reported *via* [3+2]-cycloaddition of sulphonyl/phosphoryl azides **12**, various amines **13** and ynamides **11** in the presence of CuI as catalyst and chloroform as solvent (Scheme 4). This reaction showed diastereoselectivity with tertiary amines and phosphoryl azides.¹⁹



Scheme 4. Synthesis of aminoamidines by [3+2]-cycloaddition.

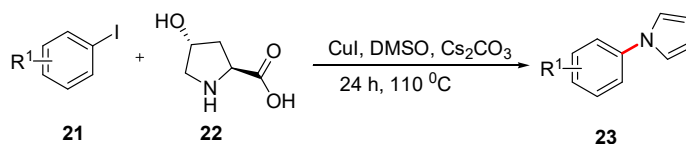
Pharmaceutically active compounds contain *N*-arylimidazole and *N*-arylamides. Imatinib **19** is an anti-cancer drug, while Sunitinib **20** is an RTK inhibitor. A variety of amides **15** was successfully *N*-arylated employing CuI as catalyst, KOH as base, and tetrabutylammonium bromide (TBAB) **18** as an additive to obtain higher yields of cross-coupled (Scheme 5). Regardless of the nature and position of substituents, several aryl iodides **16** were allowed to react with substituted amides **15** to afford high yields of *N*-phenylamides **17**.²⁰



Scheme 5. *N*-Arylation of amides employing copper(I) iodide as catalyst.

Copper(I) iodide is relatively cost-effective and readily available. In 2011, Reddy and colleagues synthesized *N*-arylated pyrroles **23** by the C–N cross-coupling of *trans*-4-hydroxy-L-proline **22** and aryl iodides **21** containing electron-rich or electron-deficient substituents at high temperature using CuI catalyst, dimethyl sulfoxide (DMSO) as solvent, and Cs₂CO₃ as base (Scheme 6). The yields of aryl iodides

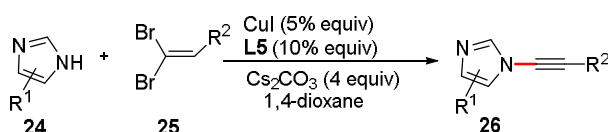
containing electron-withdrawing groups were significantly lower and the *o*-substituted aryl iodides gave the lowest yields due to steric effects.²¹



R¹=4-Me, 4-Et, 4-*t*-Butyl, 4-MeO, 3-MeO, 2-MeO, 4-BnO, 4-Cl, 4-F, 4-I, 4-NO₂, 3-NO₂, 2-NO₂, 4-Ph

Scheme 6. Cross-coupling of *trans*-4-hydroxy-L-proline with various aryl iodides.

N-Alkynyl heteroarenes were prepared **26** by cross-coupling of substituted imidazoles **24** with 1,1-dibromo-1-ene **25** in the presence of a CuI as catalyst, tetramethylethylenediamine (TMEDA) **L5** as ligand, Cs₂CO₃ as base, and dioxane as solvent (Scheme 7). The 1,1-dibromo-1-ene **25** with either electron-rich or electron-poor substituents were aminated but alkenes bearing electron-poor substituents produced the highest yields of product. Alkenes containing heteroaryl were found to be more reactive substrates.²²

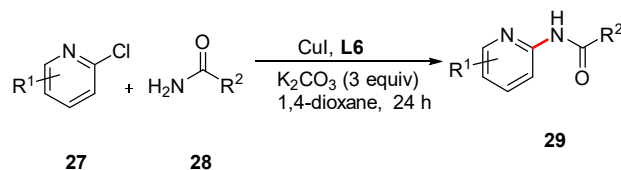


R¹=2-Me, 2-Et, 2-*i*-Propyl, 2-*n*-Propyl, 4-Me

R²=Ph, 4-MeC₆H₄, 4-ClC₆H₄, 3-BrC₆H₄, 4-CNC₆H₄, 4-MeOC₆H₄, 4-FC₆H₄, 2-Thienyl, 2-Furyl, 4-CF₃C₆H₄

Scheme 7. Synthesis of *N*-alkynyl heteroarenes *via* copper(I) iodide as catalyst.

Moreover, CuI was employed as catalyst for the chemoselective C–N coupling of 2-chloropyridine **27** containing either electron-donating groups or electron-withdrawing groups was reacted with various amides **28**, K₂CO₃ as base, 1,4-dioxane as solvent, and the ligand **L6** to afford a series of *N*-(2-pyridin-2-yl)-amides **29** (Scheme 8). Amides with electron-deficient moieties such as the nitro group produced lesser yield while a good yield of cross-coupled products was formed using nicotinamide and thiophene-2-carboxamide.

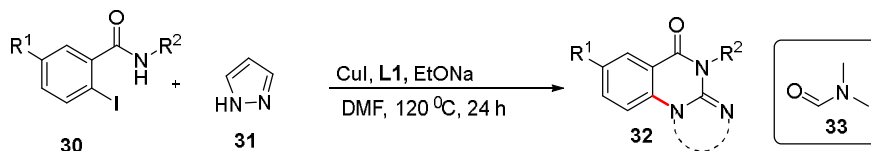


R¹=5-MeO, 3-MeO, 5-Cl, 4-I, 4-Br

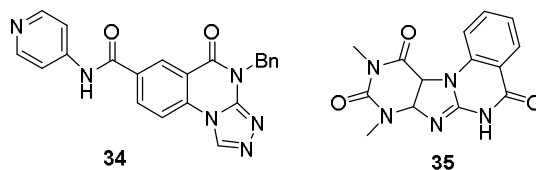
R²=4-MeOC₆H₄, 4-MeC₆H₄, 4-NO₂C₆H₄, 3,4-Cl₂C₆H₃, 3-Pyridyl, 2-Thiophenyl

Scheme 8. Synthesis of *N*-(2-pyridin-2-yl)-amides *via* C–N cross-coupling reaction.

Substituted quinazolinones have a wide range of medicinal applications such as compound **34** being effective against matrix metalloproteinase and **35** being utilized as an anti-cancer agent. Azoquinazolinones **32** were obtained by reacting a variety of 2-iodobenzamides **30** and *N*-heterocycles **31** *via* C–H activation in the presence of CuI as catalyst, 1,10-phenanthroline as ligand **L1**, dimethylformamide (DMF) **33** as solvent, O₂, and EtONa as base (Scheme 9). The 2-iodobenzamides bearing electron-rich groups such as methyl and methoxy gave the lowest yields whereas electron-deficient moieties (Cl, NO₂) gave the highest yields.^{8k}

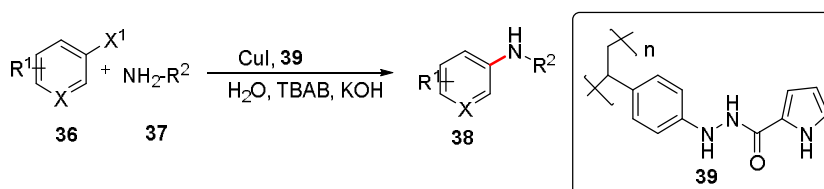


$R^1 = \text{H, Cl, Me}$
 $R^2 = \text{Bn, 4-MeC}_6\text{H}_4, \text{4-ClC}_6\text{H}_4, \text{4-NO}_2\text{C}_6\text{H}_4, \text{4-MeOC}_6\text{H}_4$



Scheme 9. Azoquinazolinones synthesis from 2-iodobenzamides and *N*-heterocycles.

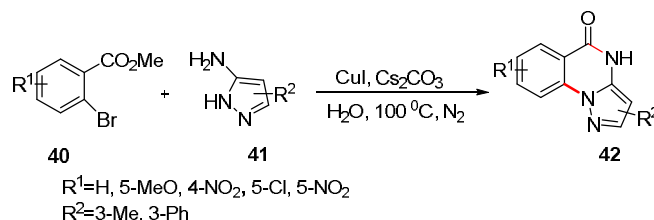
A novel catalyst, polystyrene-supported pyrrole-2-carbohydrazide (PSP) **39**, in conjunction with CuI, was employed for cross-coupling of aryl halides **36** with various amines **37** in the presence of KOH as base, TBAB and H₂O to form *N*-arylated product **38** (Scheme 10). When aryl halides **36** were replaced with methyl and methoxy groups at the *para* position rather than the *ortho* position yields were higher in this Ullmann cross-coupling.⁸ⁱ



$X = \text{C, N}$
 $X^1 = \text{Br, I}$
 $R^1 = \text{H, 4-Me, 2-MeO, 3-MeO, 4-MeO, 4-Ac, 4-NO}_2$
 $R^2 = \text{Me, } n\text{-Butyl, Cyclopentyl, Cyclohexyl, Ph, Bn, 2-MeOC}_6\text{H}_4, \text{4-MeOC}_6\text{H}_4$

Scheme 10. Ullmann cross-coupling of aryl halides and arylamines *via* CuI.

Furthermore, substituted 2-bromobenzoates **40** and a variety of 1*H*-pyrazole-5-amines **41** were cross-coupled without ligand in the presence of CuI as catalyst, Cs₂CO₃ as base, and H₂O to obtain pyrazolo[1,5-*a*]quinazolin-5(4*H*)-one derivatives **42** in quantitative yields (Scheme 11).^{8j}

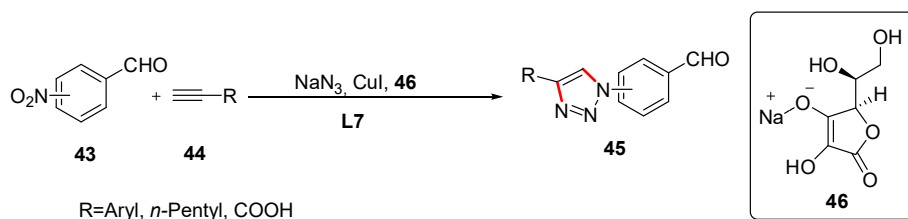


$R^1 = \text{H, 5-MeO, 4-NO}_2, \text{5-Cl, 5-NO}_2$
 $R^2 = \text{3-Me, 3-Ph}$

Scheme 11. C–N Cross-coupling of substituted 2-bromobenzoates with 1*H*-pyrazole-5-amines.

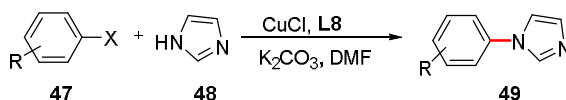
Moreover, CuI was employed to synthesize arylated 1,2,3-triazoles **45** in the presence of sodium ascorbate **46**, sodium azide, and hexamethylphosphorous triamide (HMPT) **L7** (Scheme 12). Herein, various terminal alkynes **44** reacted with *o*- or *p*-nitrobenzaldehyde **43** by aromatic nucleophilic substitution reaction

(S_NAr) reaction. Product yields were unaffected by the positions and electronic effects of substituents. However, due to steric effects, the *o*-substituted formyl group yielded comparatively lower yields.^{8j}



Scheme 12. Synthesis of 1,2,3-triazoles from nitro benzaldehyde and terminal alkynes.

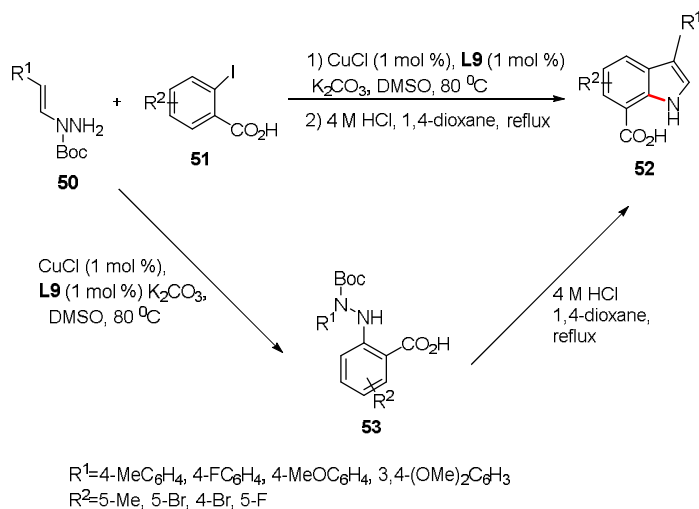
CuCl is another copper catalyst that was used for C–N cross-coupling between aryl chlorides/bromides **47** and imidazole **48** in the presence of DMF as solvent, K₂CO₃ as base, and hexamethylenetetramine (HMTA) **L8** as ligand to afford high yields of arylimidazoles **49** (Scheme 13). The reaction was free from the steric effects of aryl halides.²⁴



R=4-MeO, 4-Ac, 4-CHO, 2-MeO, 4-CH₃(CH)OH, 2-NO₂, 4-NO₂, 4-OH

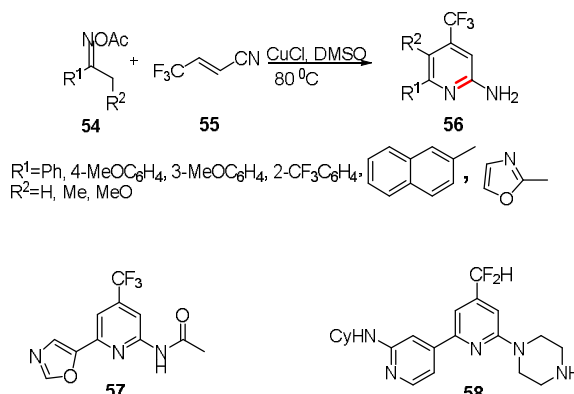
Scheme 13. Arylimidazoles synthesis from aryl halides and imidazole *via* C–N cross-coupling reaction.

Moreover, 7-carboxyindoles **52** were synthesized by using CuCl as catalyst, *N,N'*-bis((2-furyl)methyl)oxalamide (BFMO) **L9** as ligand, K₂CO₃ as base, and DMSO as solvent (Scheme 14). Before the synthesis of **52**, an intermediate **53** is formed. A variety of *o*-iodobenzoic acids **51** with electron-rich and poor groups were reacted with a variety of *N*-alkenyl hydrazines **50** protected by the *t*-butyloxycarbonyl (Boc) under reflux in 1,4-dioxane and HCl. The reaction yield was unaffected by the electronic effects of the aryl groups in both substrates.⁸¹



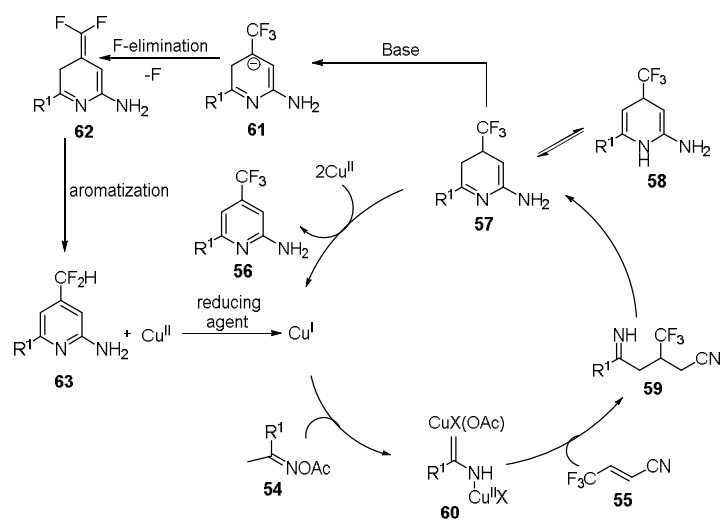
Scheme 14. Synthesis of 7-carboxyindoles using copper(I) chloride as catalyst.

Substituted 2-aminopyridines bearing trifluoromethyl group **56** are medicinally very important. For example, compounds **57** and **58** have shown activity against cancer and nervous system disorders respectively. Highly regioselective and chemoselective substituted 2-aminopyridines **56** was synthesized by employing CuCl catalyst as a Cu(I) source to cross-couple various 2-(trifluoromethyl)acrylonitrile **55** with substituted oxime esters **54** (Scheme 15). In this reaction, C–N bond construction was carried out *via* [3+3]-cycloaddition. The product yields were slightly higher with electron-donating substituents.⁸¹



Scheme 15. Copper(I) chloride catalyzed [3+3]-cycloaddition for the synthesis of substituted 2-aminopyridines.

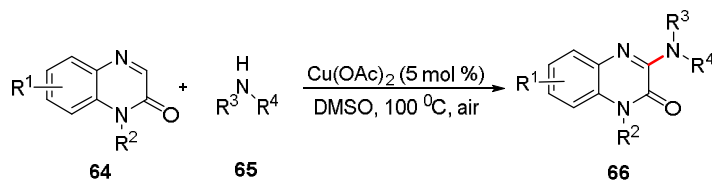
Firstly, substituted oxime esters **54** oxidized Cu(I) into Cu(II) and formed an intermediate **60**. The **59** intermediate has formed as a result of conjugate addition of **60** and β -(trifluoromethyl)acrylonitrile **55**. In the next step, dihydropyridine **57** has produced as a result of cyclization of **59**. Base abstracts a proton from **57** as a result **61** is produced. Compounds **57** and **58** exist as isomeric forms during the reaction cycle. The 4-trifluoromethyl-2-aminopyridine **56** has been generated in the next step by using two Cu(II) species. Afterwards, fluoro elimination occurred and **62** has been formed which has been tautomerized into **63**. At the same time, Cu(II) has been reduced and Cu(I) regenerated (Scheme 16).^{7f}



Scheme 16. A possible mechanism for C–N bond construction between β -(trifluoromethyl)acrylonitrile and oxime esters.

2.2. Copper acetate

The synthesis of various 3-amino-quinoxaline-2(1*H*)-ones **66** was done by reacting primary/secondary aliphatic and aromatic amines **65** with quinoxalin-2(1*H*)-ones **64** in the presence of Cu(OAc)₂ catalyst (Scheme 17). Excellent yields were observed without any additive or ligand. The electronic effects of substituents of quinoxalin-2(1*H*)-ones **64** did not affect reaction yields. On the other hand, diethylamine and 2-methylpiperidine produced a lower yield due to steric effects.²⁵



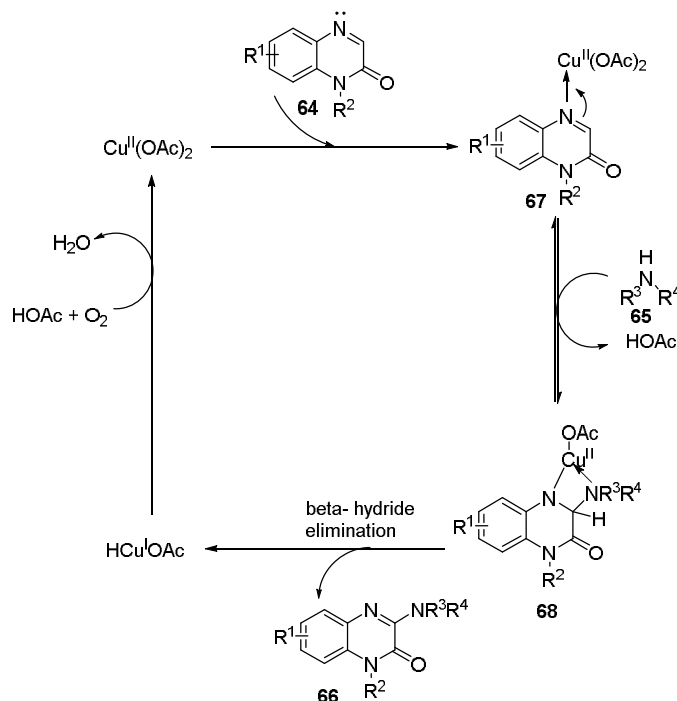
R¹=Me, Cl

R²=H, Bn, CO₂Et, 4-MeOBn

R³=R⁴=H, 4-CF₃C₆H₄, *i*-Propyl, 4-MeOBn, 4-TolylBn, Ph(CH)Me, 2-MeBn, *n*-Propyl, Cyclohexyl

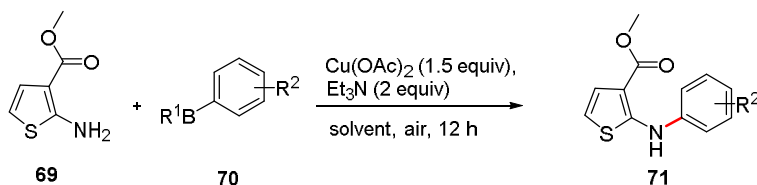
Scheme 17. Synthesis of 3-amino-quinoxaline-2(1*H*)-ones by reacting quinoxalin-2(1*H*)-ones and amines.

The Cu(II) interacted with the imine moiety of **64** in the first step of the reaction mechanism, resulting in the formation of **67**, followed by the nucleophilic attack of amine **65** on activated imine to give σ^H-adduct **68**. The required product **66** was then generated along with Cu(I) species by β-H elimination. Cu(I) was finally reoxidized to Cu(II), which initiated the next cycle (Scheme 18).²⁵



Scheme 18. A possible mechanism for the formation of 3-amino-quinoxaline-2(1*H*)-ones by copper(II) acetate C–N cross-coupling.

The thiophene moiety is very important as the compounds containing this moiety have considerable intrinsic electronic properties and therefore, can be used in field-effect transistors, photovoltaic devices and light-emitting diodes.²⁶ Thiophene compounds also have wide pharmaceutical applications.²⁷ Methyl-2-aminothiophene-3-carboxylate **69** was used as electrophilic partners and a variety of aryl boronic acids/salts of potassium aryl trifluoroborate **70** as nucleophilic partners to form alkyl(phenylamino)thiophenecarboxylate derivatives **71** in the presence of Et₃N as base, Cu(OAc)₂ as catalyst, dichloroethane/toluene/water as solvent and air at room temperature (Scheme 19). It was reported that reaction yield was independent of the electronic effects of boronic acids. A variety of functional groups was best tolerated under reaction protocol.²⁸



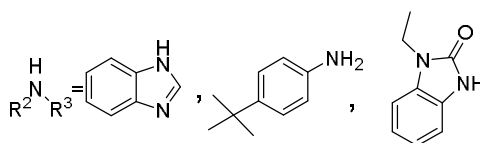
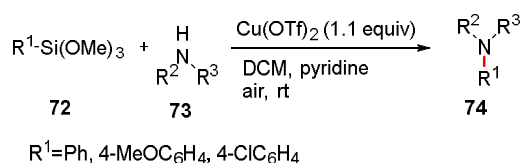
R¹=(OH)₂, KF₃

R²=H, 2-CO₂Me, 2-Me, 3-Me, 3-Cl, 3-F, 3-CO₂Me, 4-*t*-Butyl, 3-Vinyl, 4-I, 4-CF₃, 4-*i*-Propyl, 4-F, 3-CN, 3-Formyl

Scheme 19. *N*-Arylation via Chan-Lam cross-coupling reaction for the synthesis of alkyl(phenylamino)thiophene carboxylate.

2.3. Copper triflate

Lam and co-workers employed Cu(OTf)₂ catalyst for C-N cross-coupling of vinyl/aryl siloxane **72** and cyclic amines **73** in the presence of dichloromethane (DCM) solvent at room temperature to afford a variety of substituted amines **74** (Scheme 20). The best yield came from aryl siloxane with a 4-methoxy group but least with chloro group at the *para* position. The reaction was significant because *N*-arylation could be accomplished without a base, as a result, the most sensitive functional groups could be best tolerated.²⁹

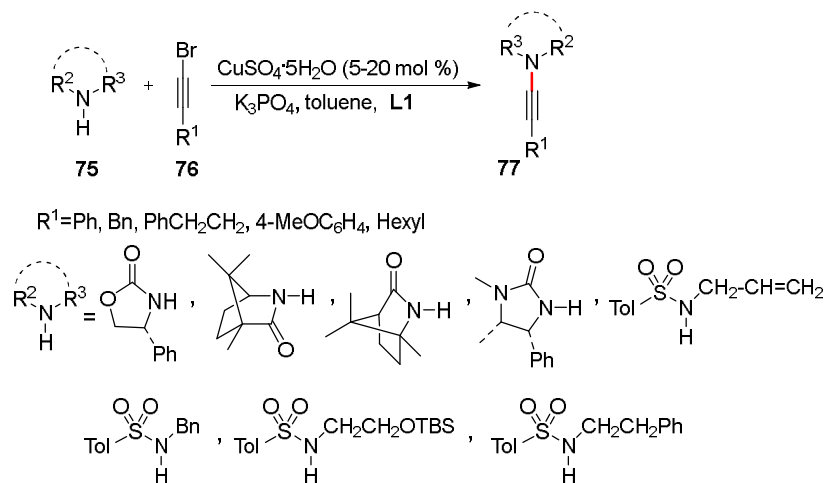


Scheme 20. Copper(II) triflate catalyzed reaction between siloxane and different cyclic amines.

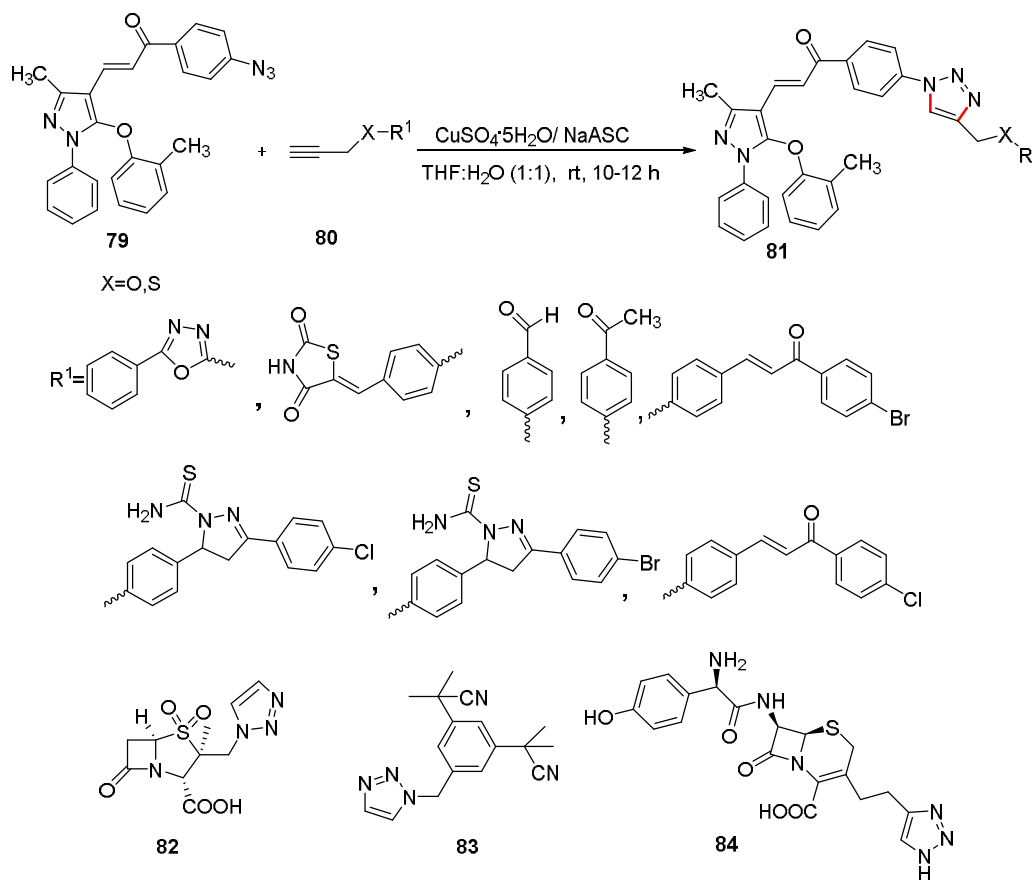
2.4. Copper sulphate

CuSO₄·5H₂O as catalyst, 1,10-phenanthroline **L1**, K₃PO₄ as base, and toluene solvent were employed to prepare a range of substituted ynamides **77** by cross-coupling between various aromatic/heteroaromatic amides **75** and alkynyl bromides **76** (Scheme 21). Sulphonyl ynamides were also synthesized in good yields and with a good functional group tolerance.³⁰

Compounds with 1,2,3-triazole functionality are biologically very significant such as cefatrizine **82**, tazobactam **81** are used as antibiotics and anastrozole **83** and **84** as an anticancer drug against breast cancer. Regioselective C-N bond was formed between aryl/heteroaryl substituted terminal alkynes **79** and pyrazole having azide moiety **78** in the presence of CuSO₄ catalyst by 1,3-dipolar cycloaddition to afford substituted triazoles **80**. The synthesized analogues triazoles show anti-bacterial activity (Scheme 22).³¹

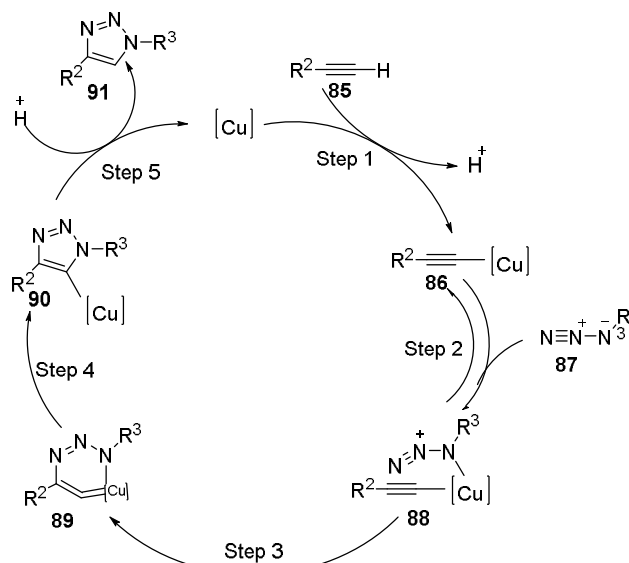


Scheme 21. Synthesis of substituted ynamides using $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ as catalyst.



Scheme 22. Regioselective synthesis of biologically active substituted triazoles.

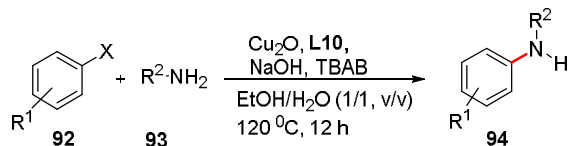
The Cu(II) derived from $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ was reduced to Cu(I) in the presence of sodium ascorbate (NaASC). Firstly, Cu(I) was coordinated by terminal alkyne **85** to form an intermediate **86**. The Cu(III) metallacycle **88** was generated in the next step as a result of azide **87** reactions with **86**. Copper triazolyl **89** was formed in the next step as a result of ring contraction. Subsequently, intermediate **90** was formed. Afterwards, protonolysis generated the product **91** (Scheme 23).³¹



Scheme 23. A general mechanism for copper-catalyzed synthesis of triazoles.

2.5. Copper oxide

Furthermore, Cu_2O catalyst was used in addition to ligand **L10**, TBAB, NaOH and EtOH/ H_2O to cross-couple cyclic/acyclic amines **93** with various aryl halides **92** bearing electron-donating groups or electron-withdrawing groups to afford *N*-arylamines **94** in this Ullmann-type reaction (Scheme 24). Aryl iodides outperformed bromides in terms of yields. Aryl chlorides did not react with amines but yields were encouraging regardless of whether aryl iodides were substituted with electron-poor or electron-rich groups. When non-aromatic amino alcohol was one of the reacting partners in this chemoselective reaction only an *N*-arylated product **94** was obtained.³²



$\text{X} = \text{Br}, \text{I}$

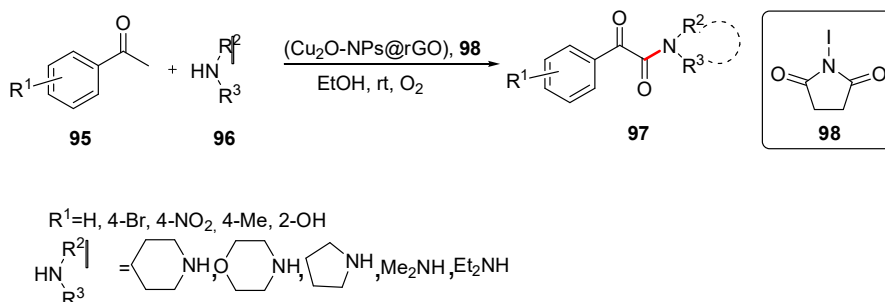
$\text{R}^1 = 4\text{-MeO}, 4\text{-Me}, 3\text{-MeO}, 4\text{-Ac}, 4\text{-Cl}, 4\text{-CF}_3, 4\text{-Cl}, 4\text{-NO}_2, 2\text{-NH}_2$

$\text{R}^2 = \text{H}, \text{C}_4\text{H}_9, \text{CH}_2\text{CH}_2\text{OH}, \text{CH}_2\text{CH}_2\text{CH}_2\text{OH},$

Scheme 24. Copper(I) oxide catalyzed *N*-arylation by reaction of amines and aryl halides.

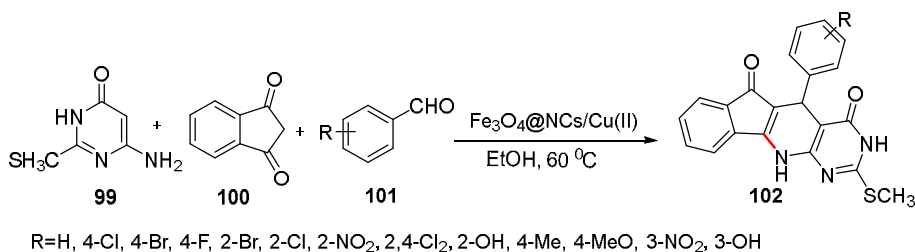
A new catalyst system Cu_2O nanoparticles on reduced graphene oxide ($\text{Cu}_2\text{O-NPs@rGO}$) was

employed to synthesize α -keto amides **97** by the reaction of cyclic/acyclic secondary amines **96** with acetophenones **95** bearing either electron-donating or withdrawing. This oxidative cross-coupling was done at room temperature in the presence of O_2 , and *N*-iodosuccinimide **98** (Scheme 25). Cyclic amines outperformed as compared to acyclic amines in terms of yields. One important feature of the reaction is the reusability of the catalyst after it has been removed from the reaction mixture, washed with H_2O , EtOH, and dried in a vacuum.³³



Scheme 25. C–N Bond formation by reaction of cyclic/acyclic secondary amines and acetophenones.

Furthermore, various indenopyrido[2,3-*d*]pyrimidines **102** were prepared by employing a reusable magnetic nano-catalyst (Scheme 26). In this reaction, the cross-coupling reaction of a variety of substituted aldehydes **101**, 1,3-indanedione **100**, and 6-amino-2-(methylthio)pyrimidin-4(3*H*)one **99** showed cross-coupling in the presence of a biocatalyst Fe_3O_4 @nano-cellulose/Cu(II) (Fe_3O_4 @NCs/Cu(II)). This catalyst could be reused and recovered by a magnet as a physical method. Both of the electron-donating or withdrawing moieties afforded products in excellent yields.³⁴



Scheme 26. C–N Cross-coupling between aldehydes, 1,3-indanedione and 6-amino-2-(methylthio)pyrimidin-4(3*H*)one.

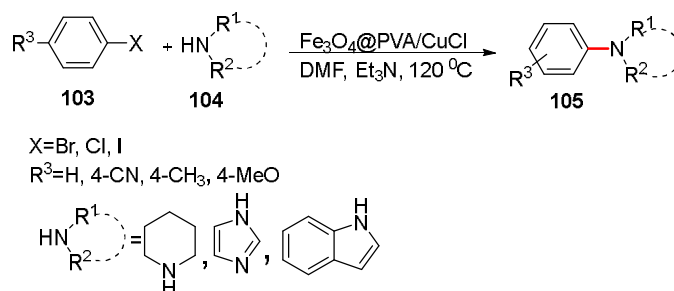
Herein, the construction of the C–N bond was reported by reacting a variety of aryl halides **103** and secondary amines **104** in the presence of magnetic polyvinyl alcohol nanocomposite (Fe_3O_4 @PVA/CuCl) as catalyst and Et_3N as base to afford the *N*-heterocycles **105** (Scheme 27). The catalyst was prepared by the coordination reaction of Fe_2O_3 with CuCl. The importance of reaction lies in the reusability of the catalyst. *N*-Arylation was done in excellent yields whether the aryl halides **103** bearing electron-poor or -rich groups in Ullmann-type reaction. However, aryl bromides gave the best yields than chlorides and iodides.³⁵

Various *N*-arylimidazoles **108** were synthesized in the presence of $[Cu(OH).TMEDA]_2Cl_2$ catalyst by reacting various aryl boronic acids **106** with substituted imidazoles **107** (Scheme 28). However, the replacement of nitrogen with oxygen gave no product. *o/p*-Tolylboronic acid gave quantitative yields while *o*-methoxyphenylboronic acids gave minimum yields which may be due to their decomposition.³⁶

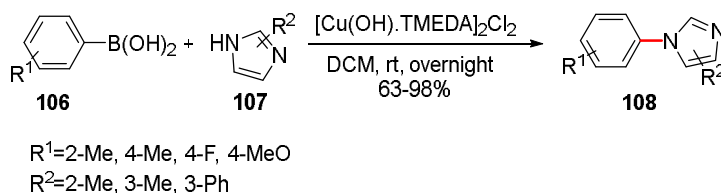
2.6. Copper MOF

Copper metal-organic frameworks (Cu(I)-MOF) were used as catalysts for the cross-coupling of

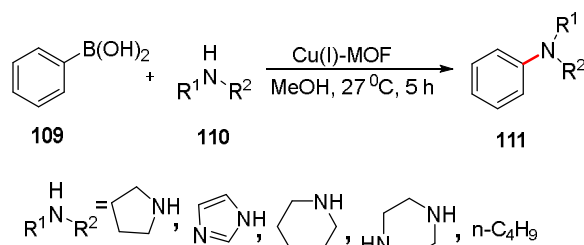
phenylboronic acid **109** with aromatic/heteroaromatic/aliphatic amines **110** to afford *N*-arylated products **111** (Scheme 29). No side product was observed. The reusability of catalysts with the same activity demonstrated the significance of the reaction.³⁷



Scheme 27. Ullmann-type C–N cross-coupling between *N*-heterocycles and aryl halides.



Scheme 28. Copper-catalysed *N*-arylation of imidazoles.

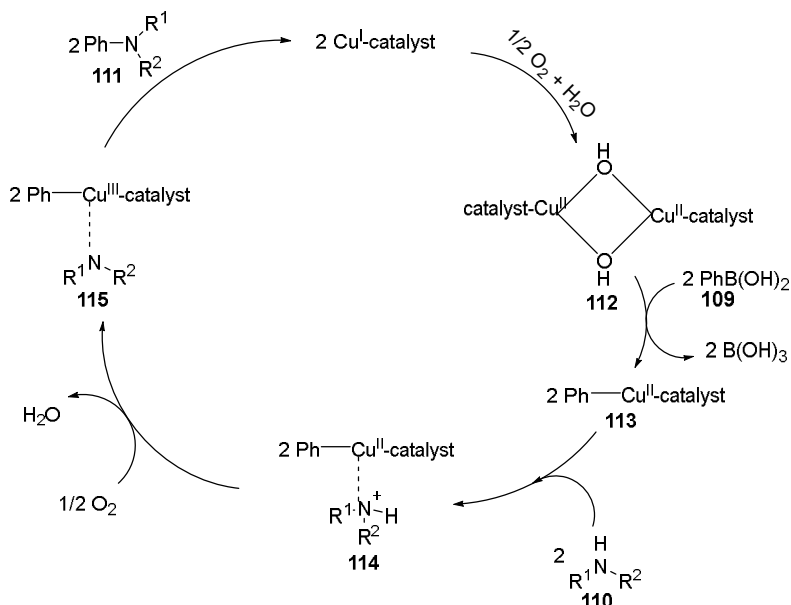


Scheme 29. Cu(I)-MOF Catalysed C–N bond formation between phenylboronic acid and various amines.

In the first step, CuI was oxidized to bis-hydroxy Cu(II) intermediate **112**. Transmetalation of phenylboronic acid with **112** resulted in the formation of a new intermediate **113**. When amine coordinated with **113**, the species **114** formed. In the presence of O₂, transition state **114** transformed into **115**, and Cu(II) oxidized to Cu(III). In the last step, C–N coupled product **111** formed as a result of reductive elimination (Scheme 30).³⁷

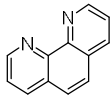
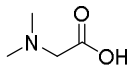

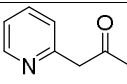
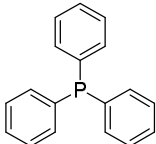
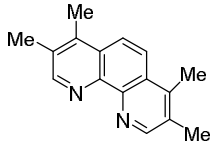

3. C–O cross-coupling

Diaryl ethers are very important moieties that find their applications in life science industries as well as polymers structures.³⁸ These diaryl ethers are also present in medicines like antibiotic vancomycin and anti-HIV chloropectins which exhibit good physiological activities.³⁹ Diaryl ethers are synthesized by C–O cross-coupling reactions in the presence of Cu catalyst.⁴⁰ Various important heterocycles such as xanthenes, benzoxazoles are prepared by C–O cross-coupling reactions using Cu as catalyst.^{8g,41} Compounds with diaryl ether functionality show antifungal and antibacterial activities such as tetramethylmagnolamine and piperazinomycin.⁴² CuBr and copper(I) acetate have been used as excellent catalysts for C–O cross-coupling reactions (Table 2).



Scheme 30. A general mechanism for the creation of a C–N bond using copper as catalyst.

Table 2. List of ligands used in C–O cross-coupling.

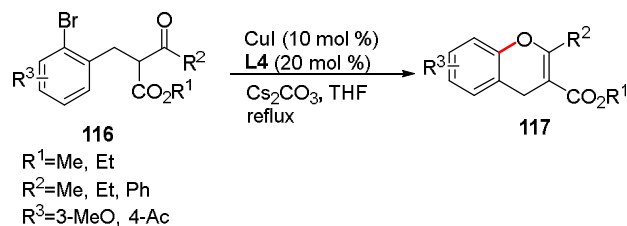
L1	1,10-Phenanthroline		L13	Dimethylglycine	
L4	Dimethylethylenediamine (DMEDA)		L14	(2-Pyridyl)acetone	
L11	Triphenylphosphine		L15	3,4,7,8-Tetramethyl-1,10-phenanthroline	
L12	Oxazolidin-2-one				

3.1. Copper halides

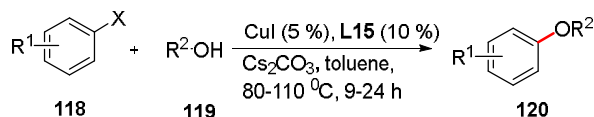
The chemoselective reaction was done to form a six-membered ring *via* intramolecular C–O cross-coupling of 1,3-dicarbonyls **116** bearing aryl bromide functionality by employing CuI catalyst in the presence ligand **L4** and Cs₂CO₃ base to afford alkyl chromene carboxylate derivatives **117** (Scheme 31). Hence, *O*-arylation occurred in encouraging yields whether substrate was substituted with electron-rich or deficient groups.⁴³

A variety of primary/secondary cyclic/acyclic benzylic or allylic alcohols **119** was cross-coupled with various aryl halides **118** in the presence of CuI catalyst, ligand **L17**, and Cs₂CO₃ base to form diaryl ether analogues **120** (Scheme 32). These reaction yields were independent of steric effects as well as electronic effects of substituted aryl halides. Cross-coupling reaction preferably occurred at aryl iodides rather than bromides and chlorides. The use of molecular sieves such as functional groups which were water-sensitive

could be easily tolerated.⁴⁴ Due to less coordination ability, primary alcohols could be selectively cross-coupled as compared to secondary alcohols. Secondary acyclic alkyl alcohols reacted more efficiently with aryl halides than secondary cyclic alkyl alcohols.



Scheme 31. Synthesis of alkyl chromene by the intramolecular C–O cross-coupling of 1,3-dicarbonyls.



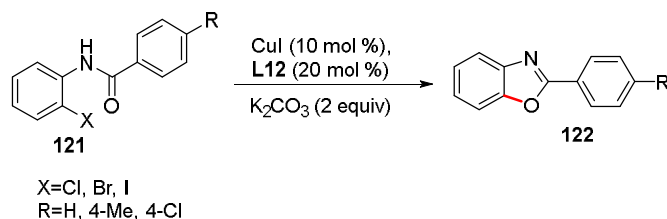
X=Br, I

R¹=4-MeO, 2-Me, 2-MeO, 2-Cl, 4-F, 4-Br, 4-Cl, 4-NH₂, 4-(2-Furyl), 3-CN, 4-CF₃, 4-Me, 3-MeO

R²=Me, Et, Bn, Hexyl, Cyclohexyl, Cyclopentyl

Scheme 32. Copper(I) iodide catalyzed ether formation.

Furthermore, benzoxazoles **122** were synthesized as a result of intramolecular cyclization of various 2-halo amides **121** in the presence of CuI as catalyst, K₂CO₃ as base and **L12** as ligand (Scheme 33).⁴¹



Scheme 33. Intramolecular C–O cross-coupling for benzoxazoles synthesis.

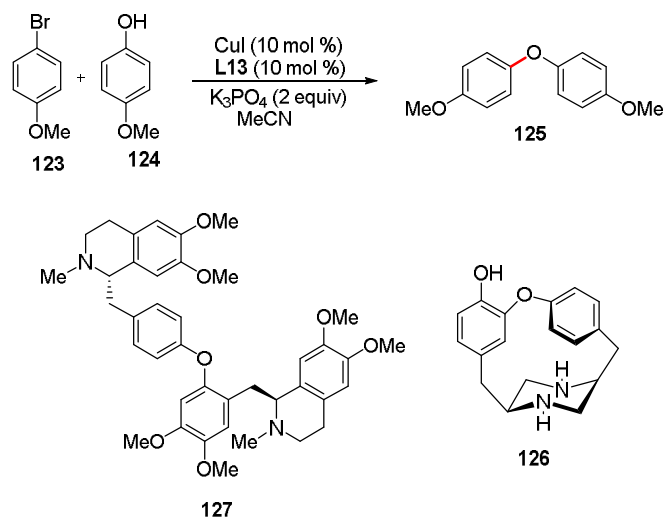
Compounds with diaryl ether functionality show antifungal and antibacterial activities such as tetramethylmagnolamine **127** and piperazinomycin **126**.^{42b} Diaryl ethers **125** were synthesized by cross-coupling of phenols **124** with aryl bromide **123** substituted with methoxy group in the presence of K₃PO₄ as base, **L13** as ligand and CuI as catalyst (Scheme 34).⁴⁰

CuBr was used as catalyst in the presence of ligand **L14**, Cs₂CO₃ base and DMSO solvent to cross-couple various phenols **129** with aryl/heteroaryl halides **128** bearing electron-donating groups or electron-withdrawing groups to obtain quantitative yields of substituted diaryl ether derivatives **130** (Scheme 35).⁴⁵ However, reaction yields were affected by steric hindrance.⁴⁶

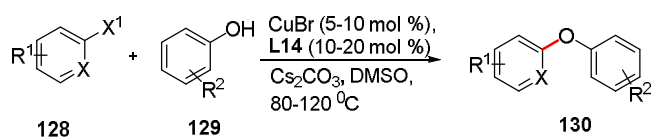
Moreover, various cyclic/acyclic 1,3-dicarbonyls **132** were reacted with aryl propionaldehyde **131** in the presence of air as an oxidant, acetic acid and CuBr catalyst at room temperature to form substituted furan derivatives **133** (Scheme 36). Cyclization was completed by the formation of a 2-furyl carbene intermediate. This reaction was regioselective as well as chemoselective to form C–O coupled product in two steps. Various functional groups and steric hindrance were best tolerated.^{8h}

In the first step, dehydration of alkynyl aldehyde **131** and dicarbonyls **132** led to the intermediate **133**, which then generated another intermediate **134** as a result of coordination to Cu(I) by the carbonyl oxygen

and alkyne group. In the next step, 2-furyl carbene intermediate **135** was formed when oxygen atom attacked as a nucleophile on C4. In the last step, due to the presence of air, oxidation occurred to give C–O coupled product **136** (Scheme 37).^{8h}



Scheme 34. Copper(I) iodide catalyzed synthesis of diaryl ether.

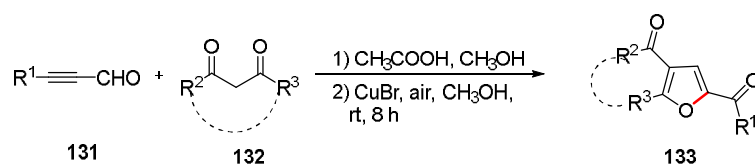


X=CH, N

X¹=Br, Cl, I

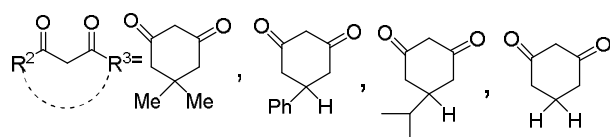
R¹=H, 4-MeO, 4-CF₃, 4-CN, 2-Ac, 4-NO₂, 2-Ac, 3,5-Me₂, 4-NH₂, 4-CO₂Me, 4-CH₂OH

Scheme 35. Cross-coupling of phenols with aryl/heteroaryl halides.

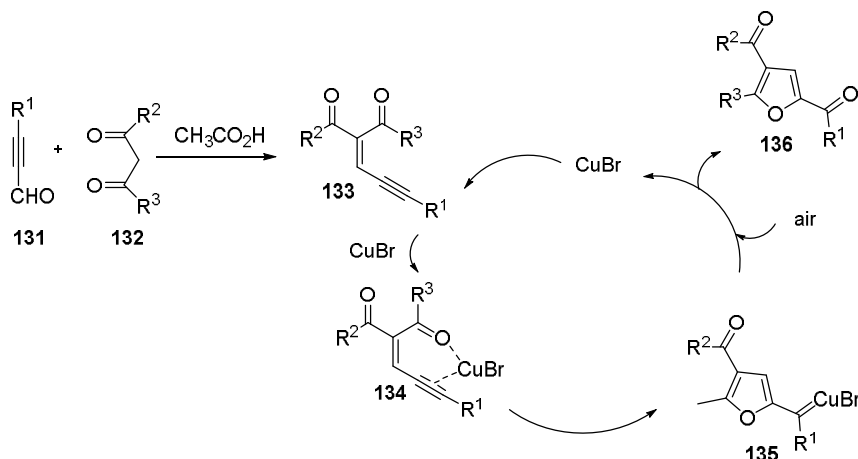


R¹=Ph, (CH₂)₄CH₃

R², R³=Me, MeO, EtO, *t*-BuO, CH₂Cl, *t*-Bu, C(CH₃)₃

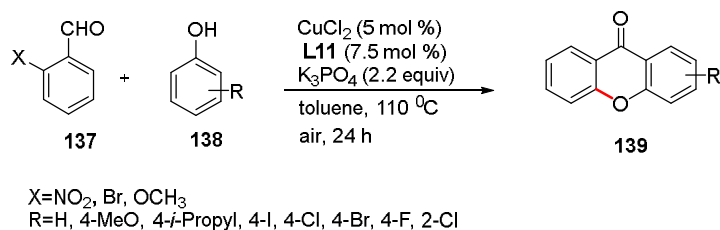


Scheme 36. Copper(I) bromide catalyzed synthesis of furan derivatives by intramolecular C–O cross-coupling.



Scheme 37. Plausible mechanism for copper(I) bromide catalysed synthesis of furan derivatives by intramolecular C–O cross-coupling.

The synthesis of various substituted xanthenes was reported by using CuCl_2 catalyst in the presence of ligand **L11**, air, and K_3PO_4 as base. A variety of phenols **138** was reacted with *o*-substituted aldehydes **137** to afford xanthen-9-one analogues **139** (Scheme 38). Phenols with electron-deficient groups like CN, NO_2 gave no reaction while electron-rich moieties gave comparatively better yields. The *o*-substituted phenols gave minimum yields due to steric effects. Pre-activation of aldehydes was not required for this reaction depicted the importance of this reaction protocol. The *O*-acylation was maximum in the case of nitro substituted aryl aldehydes.^{8g}



Scheme 38. Synthesis of xanthen-9-one analogues by the reaction of *o*-substituted aldehydes with phenols.

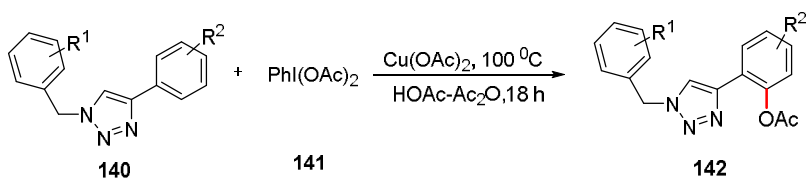
3.2. Copper acetate

C–O bond formation was reported *via* C–H bond activation in the presence of $\text{Cu}(\text{OAc})_2$ catalyst. The 1-benzyl-1,2,3-triazoles **140** substituted with various electron-donating groups or electron-withdrawing groups were cross-coupled with $\text{PhI}(\text{OAc})_2$ **141** in a regioselective reaction to afford the acetoxylation product **142** (Scheme 39). A variety of functional groups was best tolerated during this acetoxylation reaction. The electron-poor substituents gave comparatively less yields of C–O coupled products.^{1f}

In the first step, an intermediate **144** in cyclometalated form was produced as a result of an electrophilic attack of $\text{Cu}(\text{II})$ on the phenyl ring of the substrate **143**. In the next step $\text{Cu}(\text{III})$ intermediate **145** was formed as a result of oxidation followed by reductive elimination of **145** to generate the required C–O coupled product **146** and $\text{Cu}(\text{I})$. In the last step $\text{Cu}(\text{II})$ was produced as a result of oxidation of $\text{Cu}(\text{I})$ by $\text{PhI}(\text{OAc})_2$ in the presence of Ac_2O (Scheme 40).^{1f}

Intramolecular cyclization of various 3-arylcoumarins substituted with 2-hydroxy group **147** was taken place by cross dehydrogenative coupling reaction in the presence of $\text{Cu}(\text{OAc})_2$ as catalyst and ligand **L1**, afforded good yields of furanyl coumarins **148** (Scheme 41). Various functional groups like polyhydroxy

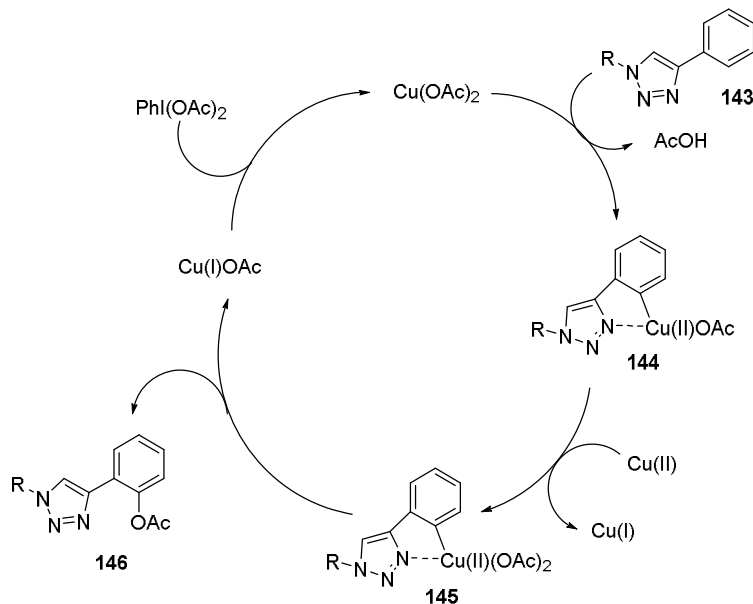
and methoxy were best tolerated.⁴⁷



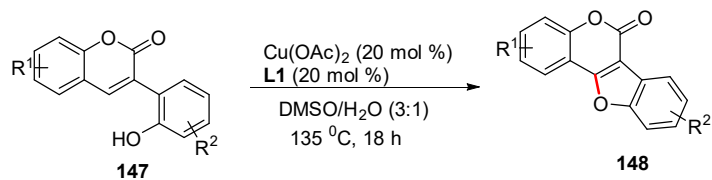
R¹=H, 4-Me, 3-Me, 2-Br, 3-Cl, 4-Cl, 4-NO₂, 4-MeO

R²=2-Me, 3-F, 4-Me, 3-Me

Scheme 39. Synthesis of acetoxytriazole derivatives in the presence of copper(II) acetate catalyst.



Scheme 40. A plausible mechanism for copper(II) acetate catalyzed C–O cross-coupling.



R¹=H, 7-OH, 7-MeO, 6-Cl

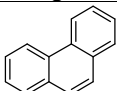
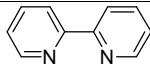
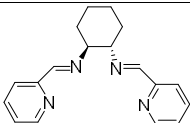
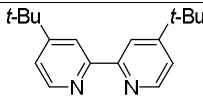
R²=H, 5-MeO, 4-MeO, 4-OH

Scheme 41. Synthesis of furanyl coumarins by intramolecular C–O cross-coupling.

4. C–S cross-coupling

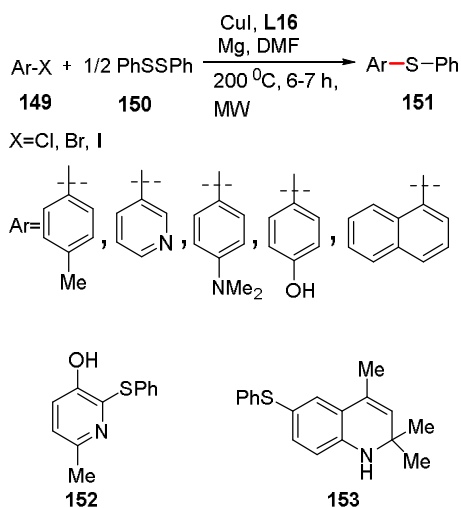
The C–S cross-coupling reactions are catalyzed by inexpensive, readily available and air-stable CuI catalyst to get better yields of cross-coupled products. This system was used to obtain a wide variety of

electronically assorted, aryl, alkyl and heterocyclic sulphides in a short time in excellent yields.⁴⁸ As C–S moiety is present in many naturally occurring compounds, medicines and synthetically important substances.^{48,49} The C–S cross-coupling reactions catalyzed by Cu are useful for the formation of the drug dapsone used to treat leprosy. This was obtained in excellent yields by a chemoselective method.⁴⁸ Synthetically useful unsymmetrical dibenzothiophenes (DBTs) were also prepared by a C–S oxidative cross-coupling reaction in the presence of Cu catalyst.⁵⁰ The ligands which can be used in C–S cross-coupling are listed in Table 3.

Table 3. List of ligands used in C–S cross-coupling.					
L2	Phenanthrene		L17	2,2'-Bipyridine	
L16	(1E,1'E)-N,N'-((1S,2S)-Cyclohexane-1,2-diyl)bis(1-(pyridin-2-yl)methanimine)		L18	4,4'-Di-tert-butyl-2,2'-bipyridine	

4.1. Copper halide

The C–S bond construction was established between diphenyl disulphides **150** and aryl/heteroaryl halides **149** in the presence of Mg metal, CuI as catalyst and ligand **L16** under microwave heating to get encouraging yields in a short time to afford diaryl thioethers **151** (Scheme 42). By heating, in the microwave, no side reaction was observed due to equal energy transfer to reacting molecules. Important antioxidants having C–S bonds **152**, **153** were also prepared in good yields.⁵¹

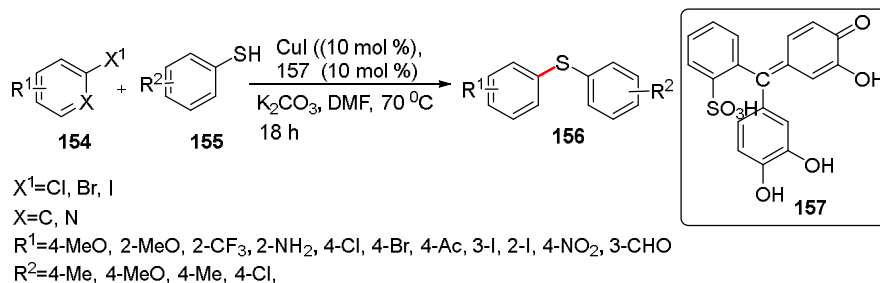


Scheme 42. Synthesis of diarylthioethers using copper(I) iodide catalyst.

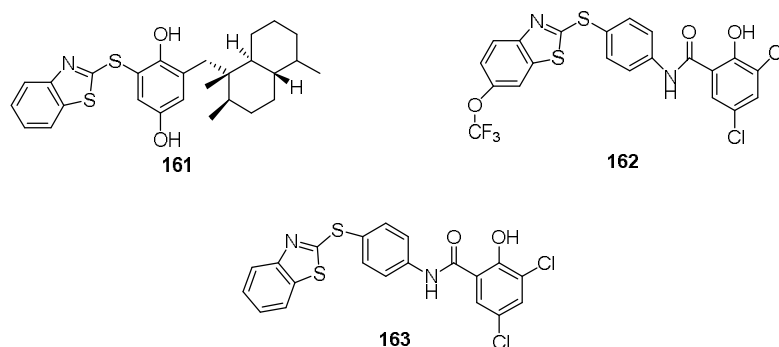
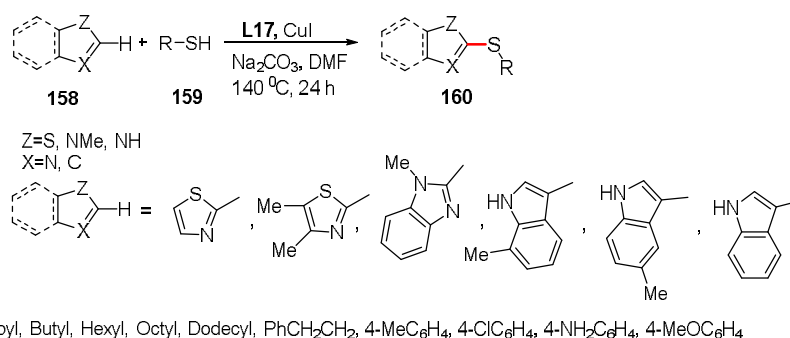
Noteworthy, a new catalyst system CuI and catechol violet (CV) **157** was employed to cross-coupled various aryl/heteroaryl halides **154** bearing electron-rich or electron-poor moieties with aromatic/aliphatic thiols **155** to form diaryl thioethers **156** in excellent yields (Scheme 43). Cheap and readily available catalyst, the absence of any phosphine ligand depicted the economic importance of reaction. The reaction yields were independent of the electronic effects of both substrates. The reaction took place selectively at iodine position if the aryl halide was substituted with Br and Cl atoms in addition to I.⁵²

Cathepsin-D inhibitor **161**, avarol-3'-thiobenzothiazole **162** are biologically important compounds that

bear substituted 2-mercapto-1,3-benzothiazole functionality. A variety of 2-mercaptobenzothiazoles **160** was synthesized by direct thiolation *via* C-H bond activation. The cross-coupling of various aromatic/aliphatic thiols **159** with *N*-heterocycles **158** in the presence of Na₂CO₃ base, CuI catalyst and bipyridyl ligand **L17** to afford arylated *N*-heterocycles **160** in maximum yields (Scheme 44). Cathepsin-D inhibitor analogue **163** was also prepared by using above mentioned reaction protocol. During the reaction mechanism, a reactive intermediate [(L)Cu(SR)] was formed instead of the Cu-thiazole complex which was responsible for organic transformation. Various functional moieties were best tolerated under reaction protocol depicted the importance of reaction. Yields were good under an anaerobic environment as O₂ was useful in the abstraction of hydrogen atoms.⁵³



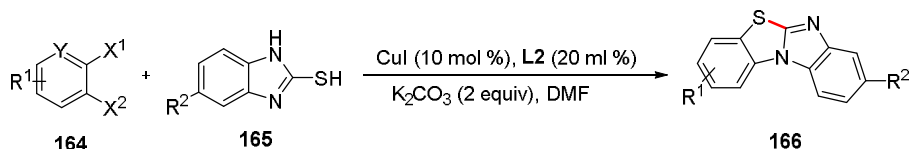
Scheme 43. S-Arylation of thiols by using aryl/heteroaryl halides.



Scheme 44. Synthesis of various 2-mercaptobenzothiazoles by using copper as catalyst.

Moreover, various 2,5-dialkyl benzo[*d*]isothiazol-3(*2H*)-ones **166** were synthesized in the presence of CuI catalyst, ligand **L2** and K₂CO₃ base by cross-coupling dihaloarenes **164** bearing electron-donating

groups or electron-withdrawing groups and 2-mercaptobenzimidazoles **165** to afford C–S cross-coupled product (Scheme 45). The electron-rich substituents gave the best yields.^{7c}



$X^1, X^2 = \text{Br, Cl, I, NO}_2$

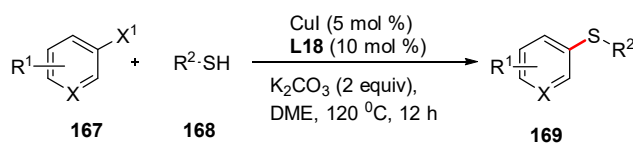
$Y = \text{CH, N}$

$R^1 = 4\text{-F, 4-Cl, 4-CN, 4-}i\text{-Propyl, 4-Me, 4-Br}$

$R^2 = \text{Me, MeO, Cl, NO}_2$

Scheme 45. C–S Cross-coupling by the reaction of 2-mercaptobenzimidazoles and dihaloarenes.

A new catalytic system CuI was developed in conjunction with 1,4-diazabicyclo[2.2.2]octane (DABCO) as ligand **L18** to cross-couple various aryl/heteroaryl halides **167** with aromatic/aliphatic thiols **168** in the presence of DME, K_2CO_3 base to get thioethers **169** in excellent yields (Scheme 46). Thiophenols substituted with electron-donating or electron-withdrawing groups gave good yields. Reaction yields were also independent by steric effects of substituents. The precursor of dapson drug **170** was also synthesized by this methodology.⁴⁸

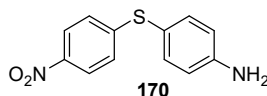


$X = \text{CH, N}$

$X^1 = \text{Br, I}$

$R^1 = 4\text{-MeO, 3-CF}_3, 2\text{-MeO, 4-CN, 4-Ac, 4-NO}_2, 4\text{-Me}$

$R^2 = 4\text{-MeC}_6\text{H}_4, 4\text{-NH}_2\text{C}_6\text{H}_4, \text{PhCH}_2\text{CH}_2, \text{Ph, } n\text{-Butyl}$



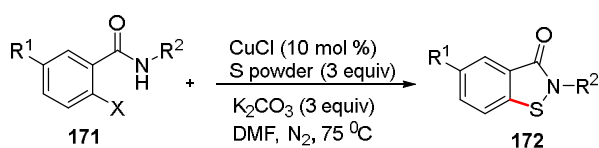
Scheme 46. Formation of thioethers by the reaction of thiols with aryl/heteroaryl halides.

Furthermore, various *N*-substituted-2-halobenzamides **171** were intermolecularly cyclized by employing CuCl catalyst, sulphur powder and K_2CO_3 base in the presence of nitrogen to form of *N*-substituted benzo[*d*]isothiazol-3(2*H*)-ones **172** (Scheme 47). These compounds were considered biologically very important as anti-fungal and anti-bacterial agents.⁵⁴ The yields were encouraging with 2-bromo- as well as 2-iodobenzamide rather than 2-chlorobenzamides.^{54b}

Compounds with dibenzothiazepines moiety are considered pharmacologically very important such as clonidine **177** a drug used to treat psychological problems whereas quetiapine fumarate **178** has been used to cure diseases of CNS. The synthesis of dibenzothiazepines **175** was synthesized by the cross-coupling of 2-aminothiophenols **173** with 2-chlorobenzaldehydes **174** in the presence of CuCl/L-proline **176** catalyst (Scheme 48).⁵⁵

Various 7-azaindoles **177** were employed as electrophilic partners and aryl boronic acids **179** having electron-rich/poor groups as nucleophilic partners and 1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) (DABSO) **178** as SO_2 donor in the presence of CuF_2 catalyst, DMF solvent, and ligand **L18** to afford product

180 in quantitative yields (Scheme 49). The reaction yield was independent by the electronic effects of substituents on aryl boronic acids. The importance of reaction lies in the high tolerance of moieties like CHO, OH and NO₂. *p*-Methoxybenzyl group was removed in the presence of mesitylene and trifluoroacetic acid (TFA).⁵⁶

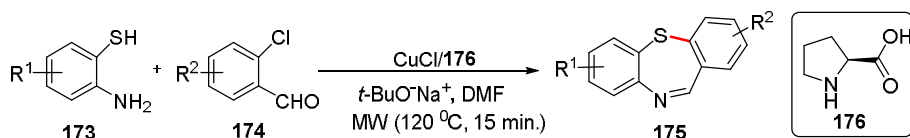


X=Cl, Br, I

R¹=H, OMe, OC₈H₁₇, NO₂, Br

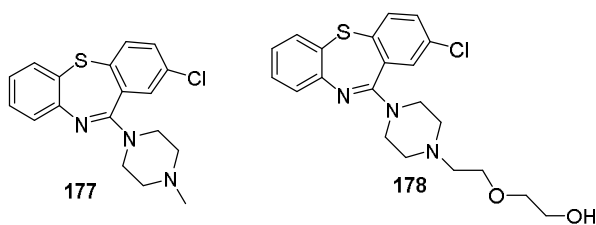
R²=4-ClC₆H₄, 4-MeC₆H₄, 2-MeOC₆H₄, 2-MeC₆H₄, 4-MeOC₆H₄, *n*-Butyl

Scheme 47. Synthesis of *N*-substituted benzo[*d*]isothiazol-3(2*H*)-ones in the presence of copper(I) chloride.

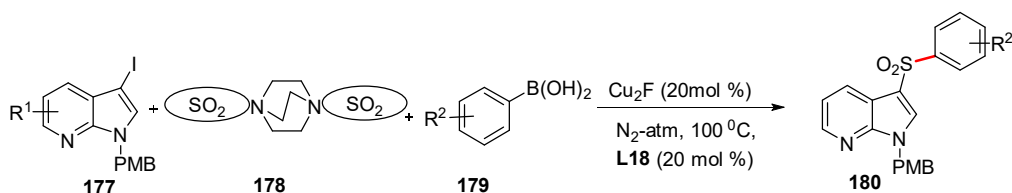


R¹=H, 4-Cl, 4-CF₃

R²=3-NO₂, 5-CF₃, 2-Cl, 3-CF₃



Scheme 48. Copper(I) chloride catalyzed synthesis of dibenzothiazepines.

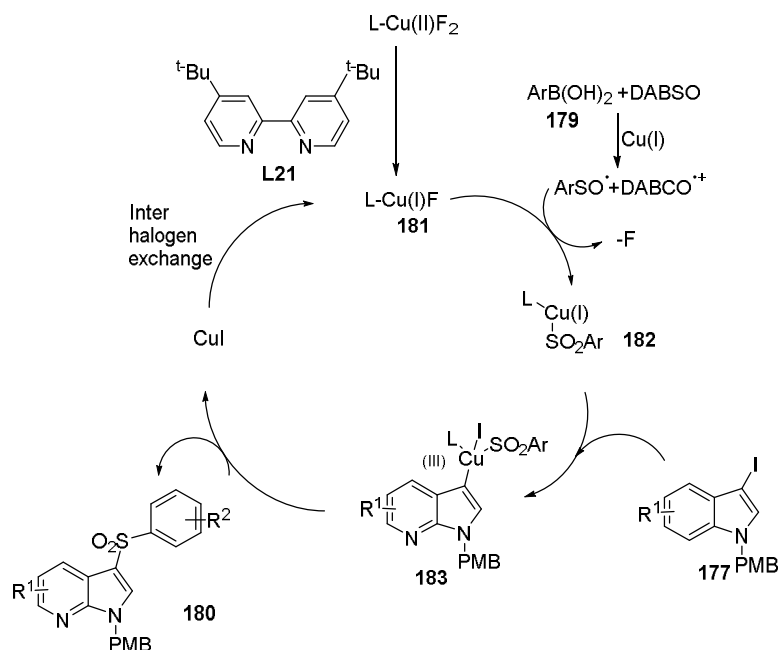


R¹=6-MeO, 6-Cl, 5-Br

R²=4-Me, 4-Br, 4-SMe, 4-MeO, 4-F, 3-Me, 4-F, 3-NO₂, 4-CHO

Scheme 49. Reaction of 7-azaindoles with aryl boronic acids by using CuF₂ catalyst.

Firstly, Cu(I) was generated due to the reduction of Cu(II) by **L18** and an intermediate **181** was formed. Aryl boronic acid **179** has reacted with DABSO resulting in the formation of sulphonyl radical. Species **182** was generated when aryl sulphonyl radical reacted with **181**. In the next step **183** was formed as a result of subsequent oxidative addition of **177**. Afterwards, reductive elimination of **183** generated desired product along with CuI. In the last step interhalogen, the exchange occurred (Scheme 50).⁵⁶



Scheme 50. A possible mechanism for C–S cross-coupling by using copper(II) fluoride.

4.2. Copper acetate

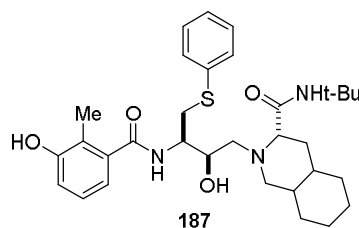
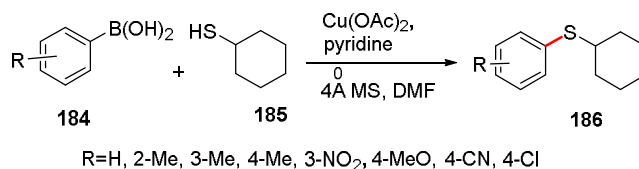
Nelfinavir **187** which is an efficient HIV protease inhibitor has aryl alkyl sulphide functionality. Cu(OAc)₂ catalyst was used in the presence of pyridine, anhydrous condition and DMF solvent to cross-coupled aryl boronic acids **184** bearings electron-rich/poor groups with alkanethiols **185** to get maximum yields of alkyl aryl thioethers **186** (Scheme 51). Electronic effects of substituted aryl boronic acids did not affect the yield and rate of reaction. However, steric hindrance resulted in less yield of product. The reaction rate was also affected by steric effects. Primary and secondary thiols also reacted in good yields but tertiary thiols gave no C–S coupled.

4.3. Copper oxide

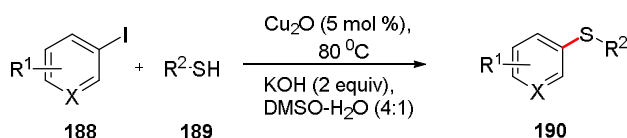
Cu₂O catalyst was used in the presence of DMSO-H₂O and KOH base to cross-coupled aryl/heteroaryl iodides **188** with aliphatic/aromatic thiols **189** to form thioethers **190** in excellent yields (Scheme 52). The electronic effects of both substrates did not affect the yield of the reaction. Reaction yields were also independent of the steric effects of both reacting molecules. Reusability of catalyst, functional group tolerance and absence of any ligand depicted the economic importance of reaction protocol.⁵⁸

5. Conclusions

Copper catalysts are evolving as potential cross-coupling reaction alternatives to palladium-based catalysts. The concept of transforming cross-coupling conversions into a sustainable process with a particular emphasis on replacing toxic, expensive, and rare palladium with earth plentiful, inexpensive, and non-toxic transition metals, is the driving force behind this new approach. Copper in particular can be considered the transition metal of choice for meeting these requirements. The significant efficacy of copper catalysts in performing aryl/heteroaryl cross-couplings has recently been revealed, according to this review. Furthermore, copper catalysts have a reactivity pattern that is distinct from palladium catalysts, in that they react efficiently with or without ligands.



Scheme 51. Synthesis of aryl alkyl thioethers by reaction of aryl boronic acids with thiols.



X=CH, N

R¹=4-Me, 4-Cl, 4-MeO, 4-Ac, 4-NO₂, 4-CF₃, 2-Me, 2-MeO

R²=4-NH₂C₆H₄, 4-MeOC₆H₄, 4-MeC₆H₄, 4-FC₆H₄, 4-ClC₆H₄, 4-BrC₆H₄, CH₃(CH₂)₁₁, Ph, 4-NO₂C₆H₄, 2-MeOC₆H₄, 2-NH₂C₆H₄, 3-MeC₆H₄, *n*-Butyl, *n*-Octyl

Scheme 52. *S*-Arylation/heteroarylation catalyzed by copper oxide to synthesize thioethers.

Acknowledgement

We acknowledge the synthetic organic chemistry laboratory of Dr. Nasir Rasool for continuous support.

References

- Kohei, T.; Miyaura, N. *Cross-Coupling Reactions* **2002**, 1-9.
 - Haolong, W.; Boshun, W. *Chinese J. Catal.* **2011**, *32*, 1129-1132.
 - You, C.; Yao, F.; Yan, T.; Cai, M. *RSC Adv.* **2016**, *6*, 43605-43612.
 - Ali, I.; Nighot, D.; Lone, M. N.; Jain, A. *Synth. Commun.* **2017**, *47*, 1175-1184.
 - Sadat-Ebrahimi, S. E.; Haghayegh-Zavareh, S. M.; Bahadorikhalili, S.; Yahya-Meymandi, A.; Mahdavi, M.; Saeedi, M., *Synth. Commun.* **2017**, *47*, 2324-2329.
 - Fu, X.; Zhao, F.; Zhao, L.; Liu, Y.; Luo, F.; Jiang, Y. *Synth. Commun.* **2017**, *47*, 2305-2312.
 - Etemadi-Davan, E.; Iranpoor, N.; Arshad, P. *Asian J. Org. Chem.* **2018**, *7*, 683-687.
 - Bottoni, A.; Calvaresi, M.; Marforio, T. D.; Miscione, G. P. *Eur. J. Org. Chem.* **2019**, *2019*, 6776-6782.
 - Sekar, G.; Sangeetha, S.; Nandy, A.; Saha, R. *Copper Catalysis in Organic Synthesis* **2020**, 395-422.
 - Salahshournia, B.; Hamadi, H.; Nobakht, V. *Polyhedron* **2020**, *189*, 114749.
- Deng, C.-L.; Xie, Y.-X.; Yin, D.-L.; Li, J.-H. *Synthesis* **2006**, *2006*, 3370-3376.
 - Xu, J.; Luo, D.-F.; Xiao, B.; Liu, Z.-J.; Gong, T.-J.; Fu, Y.; Liu, L. *Chem. Commun.* **2011**, *47*, 4300-4302.
 - Mitrofanov, A. Y.; Beletskaya, I. P. *Mendeleev Commun.* **2019**, *29*, 378-379.
- Duong, H. A.; Gilligan, R. E.; Cooke, M. L.; Phipps, R. J.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2011**, *50*, 463-466.
 - Xu, H.-Y.; Wang, S.-Y.; Jiang, R.; Xu, X.-P.; Chu, X.-Q.; Ji, S.-J. *Tetrahedron* **2012**, *68*, 8340-8346.
- Ngo, T. N.; Akrawi, O. A.; Dang, T. T.; Villinger, A.; Langer, P. *Tetrahedron Lett.* **2015**, *56*, 86-88.
 - Pham, N. N.; Dang, T. T.; Ngo, N. T.; Villinger, A.; Ehlers, P.; Langer, P. *Org. Biomol. Chem.* **2015**,

- 13, 6047-6058. c) Ngo, T. N.; Janert, F.; Ehlers, P.; Dang, T. T.; Villinger, A.; Lochbrunner, S.; Langer, P. *Org. Biomol. Chem.* **2016**, *14*, 1293-1301. d) Pham, N. N.; Janke, S.; Salman, G. A.; Dang, T. T.; Le, T. S.; Spannenberg, A.; Ehlers, P.; Langer, P. *Eur. J. Org. Chem.* **2017**, *2017*, 5554-5565. e) Pham, N. N.; Salman, G. A.; Ponce, M. B.; Dang, T. T.; Spannenberg, A.; Ehlers, P.; Langer, P. *Eur. J. Org. Chem.* **2017**, *2017*, 3865-3873. f) Nghia Pham, N.; Ali Salman, G.; Belattar, N.; Thanh Dang, T.; Ehlers, P.; Langer, P. *Eur. J. Org. Chem.* **2017**, *2017*, 989-995. g) Pham, N. N.; Parpart, S.; Grigoryan, S.; Ngo, T. N.; Dang, T. T.; Ghochikyan, T. V.; Saghyan, A. S.; Ehlers, P.; Langer, P. *Eur. J. Org. Chem.* **2017**, *2017*, 538-550. h) Hung, T. Q.; Van Tinh, D.; Do, H. N.; Tien, T. A. N.; Van Do, D.; Tran, N. H.; Van Tuyen, N.; Tan, V. M.; Ehlers, P.; Dang, T. T. *Tetrahedron* **2019**, *75*, 130569. i) Hung, T. Q.; Quan, N. M.; Van Dong, H.; Nguyen, T. D.; Anh, H. L. T.; Hung, T. Q.; Van Tuyen, N.; Tuan, N. T.; Dang, T. T.; Langer, P. *Synlett* **2019**, *30*, 303-306.
5. a) Itman, R. A.; Buchwald, S. L. *Nat. Protoc.* **2007**, *2*, 2474-2479. b) Du, Z.; Zhou, W.; Bai, L.; Wang, F.; Wang, J.-X. *Synlett* **2011**, *2011*, 369-372. c) Castillo, P.; Buchwald, S. *Chem. Rev.* **2016**, *116*, 12564-12649. d) Giri, R.; Brusoe, A.; Troshin, K.; Wang, J. Y.; Font, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2018**, *140*, 793-806.
 6. a) Dehli, J. R.; Legros, J.; Bolm, C. *Chem. Commun.* **2005**, 973-986. b) Bernini, R.; Cacchi, S.; Fabrizi, G.; Filisti, E.; Sferrazza, A. *Synlett* **2009**, *2009*, 1480-1484. c) Garcia Ruano, J. L.; Duce, S.; Alemán, J.; López-Cantarero, J.; Remuñán, M. J.; Cid, M. B. *J. Sulphur Chem.* **2009**, *30*, 370-376. d) Hierso, J.-C.; Beaupier, M.; Saleh, S.; Job, A.; Andrieu, J.; Picquet, M. *C R Chim.* **2013**, *16*, 580-596.
 7. a) Adams, N. D.; Adams, J. L.; Burgess, J. L.; Chaudhari, A. M.; Copeland, R. A.; Donatelli, C. A.; Drewry, D. H.; Fisher, K. E.; Hamajima, T.; Hardwicke, M. A. *J. Med. Chem.* **2010**, *53*, 3973-4001. b) Jacob, K.; Stolle, A. *Synth. Commun.* **2014**, *44*, 1251-1257. c) Gao, J.; Zhu, J.; Chen, L.; Shao, Y.; Zhu, J.; Huang, Y.; Wang, X.; Lv, X. *Tetrahedron Lett.* **2014**, *55*, 3367-3373. d) Forster, M.; Chaikuad, A.; Dimitrov, T.; Döring, E.; Holstein, J.; Berger, B.-T.; Gehringer, M.; Ghoreschi, K.; Müller, S.; Knapp, S. *J. Med. Chem.* **2018**, *61*, 5350-5366. e) Elsayed, M. S.; Nielsen, J. J.; Park, S.; Park, J.; Liu, Q.; Kim, C. H.; Pommier, Y.; Agama, K.; Low, P. S.; Cushman, M. *J. Med. Chem.* **2018**, *61*, 10440-10462. f) Li, X.; Yu, Y.; Qi, R.; Bai, D. *Tetrahedron Lett.* **2020**, *61*, 151858.
 8. a) Antilla, J. C.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 2077-2079. b) Quach, T. D.; Batey, R. A. *Org. Lett.* **2003**, *5*, 4397-4400. c) Thathagar, M. B.; Beckers, J.; Rothenberg, G. *Green Chem.* **2004**, *6*, 215-218. d) Guo, S. M.; Deng, C. L.; Li, J. H. *Chin. Chem. Lett.* **2007**, *18*, 13-16. e) Mousseau, J. J.; Bull, J. A.; Charette, A. B. *Angew. Chem. Int. Ed.* **2010**, *122*, 1133-1136. f) Lei, M.; Ma, L.; Hu, L. *Synth. Commun.* **2011**, *41*, 3071-3077. g) Hu, J.; Adogla, E. A.; Ju, Y.; Fan, D.; Wang, Q. *Chem. Commun.* **2012**, *48*, 11256-11258. h) Cao, H.; Zhan, H.; Cen, J.; Lin, J.; Lin, Y.; Zhu, Q.; Fu, M.; Jiang, H. *Org. Lett.* **2013**, *15*, 1080-1083. i) Huang, L.; Yu, R.; Zhu, X.; Wan, Y. *Tetrahedron* **2013**, *69*, 8974-8977. j) Zhang, X.; Gao, L.; Wang, Z.; Fan, X. *Synth. Commun.* **2015**, *45*, 2426-2435. k) Munir, I.; Zahoor, A. F.; Rasool, N.; Naqvi, S. A. R.; Zia, K. M.; Ahmad, R. *Mol. Divers.* **2019**, *23*, 215-259. l) Wei, Q.; Wang, Y.; Zhao, J.; Zhang, X.; Ma, D. *Tetrahedron* **2020**, *76*, 130794.
 9. a) Mullard, A. *Nat. Rev. Drug Discov.* **2012**, *11*, 91-96. b) Chen, D.; Chen, Q.; Liu, M.; Dai, S.; Huang, L.; Yang, J.; Bao, W. *Tetrahedron* **2013**, *69*, 6461-6467.
 10. a) Van Phuc, B.; Do, H. N.; Quan, N. M.; Tuan, N. N.; An, N. Q.; Van Tuyen, N.; Anh, H. L. T.; Hung, T. Q.; Dang, T. T.; Langer, P. *Synlett* **2021**, *32*, 1004-1008. b) Nguyen, N.-K.; Nam, D. H.; Van Phuc, B.; Nguyen, V. H.; Trinh, Q. T.; Hung, T. Q.; Dang, T. T. *Molecular Catalysis* **2021**, *505*, 111462. c) Do, H. N.; Quan, N. M.; Van Phuc, B.; Van Tinh, D.; Tien, N. Q.; Nga, T. T. T.; Hung, T. Q.; Dang, T. T.; Langer, P. *Synlett* **2021**, *32*, 611-615. d) Langer, P.; Dang, T.; Hung, T.; Do, H.; Quan, N.; Van Phuc, B.; Van Tinh, D.; Tien, N.; Nga, T.; Nguyen, V. *Synlett* **2021**, *32*, 611-615.
 11. Andersen, R. J.; Faulkner, D. J.; He, C. H.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1985**, *107*, 5492-5495. Jones, R. A., *The Synthesis, Reactivity, and Physical Properties of Substituted Pyrroles*, Wiley Online Library, **1992**.
 12. Li, L.; Zhu, L.; Chen, D.; Hu, X.; Wang, R. *Eur. J. Org. Chem.* **2011**, *2011*, 2692-2696.
 13. a) Ward, Y. D.; Farina, V. *Tetrahedron Lett.* **1996**, *37*, 6993-6996. b) Willoughby, C. A.; Chapman, K. T. *Tetrahedron Lett.* **1996**, *37*, 7181-7184. c) Batch, A.; Dodd, R. H. *J. Org. Chem.* **1998**, *63*, 872-877. d) Link, J. T.; Sorensen, B.; Liu, G.; Pei, Z.; Reilly, E. B.; Leitza, S.; Okasinski, G. *Biorg. Med. Chem.*

- Lett.* **2001**, *11*, 973-976. e) Deng, B. L.; Lepoivre, J. A.; Lemièrre, G. *Eur. J. Org. Chem.* **1999**, *1999*, 2683-2688.
14. a) Mann, G.; Hartwig, J. F.; Driver, M. S.; Fernández-Rivas, C. *J. Am. Chem. Soc.* **1998**, *120*, 827-828. b) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575-5580. c) Old, D. W.; Harris, M. C.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1403-1406.
15. Kiyomori, A.; Marcoux, J.-F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2657-2660.
16. Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727-7729.
17. Shafir, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 8742-8743.
18. Kim, J. Y.; Kim, S. H.; Chang, S. *Tetrahedron Lett.* **2008**, *49*, 1745-1749.
19. Ali, M. A.; Saha, P.; Punniyamurthy, T. *Synthesis* **2010**, *2010*, 908-910.
20. Reddy, V. P.; Kumar, A. V.; Rao, K. R. *Tetrahedron Lett.* **2011**, *52*, 777-780.
21. Kukosha, T.; Trufilkina, N.; Belyakov, S.; Katkevics, M. *Synthesis* **2012**, *44*, 2413-2423.
22. Nicolas, L.; Angibaud, P.; Stansfield, I.; Meerpoel, L.; Reymond, S.; Cossy, J. *RSC Adv.* **2013**, *3*, 18787-18790.
23. Cao, C.; Lu, Z.; Cai, Z.; Pang, G.; Shi, Y. *Synth. Commun.* **2012**, *42*, 279-284.
24. Li, Y.; Gao, M.; Wang, L.; Cui, X. *Org. Biomol. Chem.* **2016**, *14*, 8428-8432.
25. a) Garnier, F.; Yassar, A.; Hajlaoui, R.; Horowitz, G.; Deloffre, F.; Servet, B.; Ries, S.; Alnot, P. *J. Am. Chem. Soc.* **1993**, *115*, 8716-8721. b) Garnier, F.; Hajlaoui, R.; Yassar, A.; Srivastava, P. *Science* **1994**, *265*, 1684-1686. c) Garnier, F. *Angew. Chem.* **1989**, *101*, 529-533. d) Dodabalapur, A.; Torsi, L.; Katz, H. *Science* **1995**, *268*, 270-271. e) Dodabalapur, A.; Katz, H. E.; Torsi, L. *Adv. Mater.* **1996**, *8*, 853-855.
26. a) Mohan, C.; Bhargava, G.; Bedi, P. M. *J. Life Sci.* **2009**, *1*, 97-101. b) Sharma, S.; Athar, F.; Maurya, M. R.; Azam, A. *Eur. J. Med. Chem.* **2005**, *40*, 1414-1419. c) Folkes, A. J.; Ahmadi, K.; Alderton, W. K.; Alix, S.; Baker, S. J.; Box, G.; Chuckowree, I. S.; Clarke, P. A.; Depledge, P.; Eccles, S. A. *J. Med. Chem.* **2008**, *51*, 5522-5532. d) Abdelhamid, A. O., *J. Heterocycl. Chem.* **2009**, *46*, 680-686; e) Laddha, S. S.; Bhatnagar, S. P. *Biorg. Med. Chem.* **2009**, *17*, 6796-6802. f) Alagarsamy, V.; Raja Solomon, V.; Meenac, R.; Ramaseshu, K.; Thirumurugan, K.; Murugesan, S. *Med. Chem.* **2007**, *3*, 67-73. g) Wardakhan, W.; Abdel-Salam, O. M.; Elmegeed, G. A. *Acta. Pharm.* **2008**, *58*, 1-14. h) Connor, D. T.; Sorenson, R. J.; Cetenko, W. A.; Kerbleski, J. J.; Tinney, F. J. *J. Med. Chem.* **1984**, *27*, 528-530. i) Gouda, M.; Eldien, H.; Girges, M.; Berghot, M., *Med. Chem.* **2013**, *3*, 2228-2232. j) Castelli, M. P.; Casu, A.; Casti, P.; Lobina, C.; Carai, M. A.; Colombo, G.; Solinas, M.; Giunta, D.; Mugnaini, C.; Pasquini, S. *J. Pharmacol. Exp. Ther.* **2012**, *340*, 529-538. k) Patch, R. J.; Baumann, C. A.; Liu, J.; Gibbs, A. C.; Ott, H.; Lattanze, J.; Player, M. R. *Biorg. Med. Chem. Lett.* **2006**, *16*, 3282-3286.
27. Rizwan, K.; Karakaya, I.; Heitz, D.; Zubair, M.; Rasool, N.; Molander, G. A. *Tetrahedron Lett.* **2015**, *56*, 6839-6842.
28. Lam, P. Y.; Deudon, S.; Averill, K. M.; Li, R.; He, M. Y.; DeShong, P.; Clark, C. G. *J. Am. Chem. Soc.* **2000**, *122*, 7600-7601.
29. Zhang, Y.; Hsung, R. P.; Tracey, M. R.; Kurtz, K. C.; Vera, E. L. *Org. Lett.* **2004**, *6*, 1151-1154.
30. Nagaraja, M.; Kalluraya, B.; Shreekanth, T. K.; Kumar, M. S. *J. Heterocycl. Chem.* **2020**, *57*, 3642-3652.
31. Xie, J.-W.; Yao, Z.-B.; Wang, X.-C.; Zhang, J. *Tetrahedron* **2019**, *75*, 3788-3792.
32. Lu, W.; Sun, W.; Tan, X.; Wang, B.; Yang, H.; Gao, L.; Zheng, G. *Catal. Commun.* **2019**, *132*, 105806.
33. Safajoo, N.; Mirjalili, B. B. F.; Bamoniri, A. *Polycyc. Aromatic Compounds* **2019**, *41*, 1-8.
34. Hemmati, S.; Ahany Kamangar, S.; Yousefi, M.; Hashemi Salehi, M.; Hekmati, M. *Appl. Organomet. Chem.* **2020**, *34*, e5611.
35. Collman, J. P.; Zhong, M. *Org. Lett.* **2000**, *2*, 1233-1236.
36. Rani, P.; Srivastava, R. *Tetrahedron Lett.* **2014**, *55*, 5256-5260.
37. Theil, F. *Angew. Chem. Int. Ed.* **1999**, *38*, 2345-2347. Scott, S. J. *Tetrahedron* **2000**, *56*, 5045-5065. c) Kikelj, D. *Synthesis* **2006**, *2006*, 2271-2285.
38. Wolter, M.; Nordmann, G.; Job, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 973-976. Deng, H.; Jung, J.-K.; Liu, T.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 9032-9034.
39. Otto, N.; Opatz, T. *Beilstein J. Org. Chem.* **2012**, *8*, 1105-1111.
40. Ma, H. C.; Jiang, X. Z. *Synlett* **2008**, *2008*, 1335-1340.

41. a) Tamai, S.; Kaneda, M.; Nakamura, S. *J. Antibiot.* **1982**, *35*, 1130-1136. b) Lam, P. Y.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941-2944.
42. Fang, Y.; Li, C. *J. Org. Chem.* **2006**, *71*, 6427-6431.
43. Altman, R. A.; Shafir, A.; Choi, A.; Lichtor, P. A.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 284-286.
44. a) Buck, E.; Song, Z. J.; Tschaen, D.; Dormer, P. G.; Volante, R.; Reider, P. J. *Org. Lett.* **2002**, *4*, 1623-1626. b) D'Angelo, N. D.; Peterson, J. J.; Booker, S. K.; Fellows, I.; Dominguez, C.; Hungate, R.; Reider, P. J.; Kim, T.-S. *Tetrahedron Lett.* **2006**, *47*, 5045-5048.
45. Zhang, Q.; Wang, D.; Wang, X.; Ding, K. *J. Org. Chem.* **2009**, *74*, 7187-7190.
46. Song, X.; Luo, X.; Sheng, J.; Li, J.; Zhu, Z.; Du, Z.; Miao, H.; Yan, M.; Li, M.; Zou, Y. *RSC Adv.* **2019**, *9*, 17391-17398.
47. Thomas, A. M.; Asha, S.; Sindhu, K.; Anilkumar, G. *Tetrahedron Lett.* **2015**, *56*, 6560-6564.
48. a) Wirth, T., *Tetrahedron* **1999**, *55*, 1-28. b) Procter, D. J. *J. Chem. Soc. Perkin Trans. 1* **1999**, *1999*, 641-668. c) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359-1470. d) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337-2364. e) Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651-2710.
49. Qiao, Z.; Ge, N.; Jiang, X. *Chem. Commun.* **2015**, *51*, 10295-10298.
50. Kumar, S.; Engman, L. *J. Org. Chem.* **2006**, *71*, 5400-5403.
51. Ranjit, S.; Lee, R.; Heryadi, D.; Shen, C.; Wu, J. E.; Zhang, P.; Huang, K.-W.; Liu, X. *J. Org. Chem.* **2011**, *76*, 8999-9007.
52. a) Gialdi, F.; Ponci, R.; Caccialanza, P. *Mycopathol. Mycol. Appl.* **1964**, *24*, 163-171. b) Paul, R.; Punniyamurthy, T. *RSC Adv.* **2012**, *2*, 7057-7060.
53. Saha, D.; Wadhwa, P.; Sharma, A. *RSC Adv.* **2015**, *5*, 33067-33076.
54. Dar, M. O.; Bharatam, P. V.; Das, P.; Kukreti, S.; Tandon, V. *Tetrahedron* **2020**, *76*, 131337.
55. Herradura, P. S.; Pendola, K. A.; Guy, R. K. *Org. Lett.* **2000**, *2*, 2019-2022.
56. Xu, H.-J.; Zhao, X.-Y.; Fu, Y.; Feng, Y.-S. *Synlett* **2008**, *2008*, 3063-3067.