Modern Trends in the Copper-Catalyzed Synthesis of Sulfonamides

Prakash Chandra (prakash.chandra@sot.pdpu.ac.in)
Pandit Deendayal Petroleum University
Neha Choudhary
Indian Institute of Technology
Goutam K. Lahiri
Indian Institute of Technology
Debabrata Maiti
Indian Institute of Technology
Mobin Shaikh
Indian Institute of Technology

Research Article

Keywords:

Posted Date: September 13th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-2046804/v1

Modern Trends in the Copper-Catalyzed Synthesis of Sulfonamides

Prakash Chandra[a], Neha Choudhary[b], Goutam K. Lahiri[c], Debabrata Maiti[c], Mobin Shaikh*[b,d,e]

[a] *School of Technology, Pandit Deendayal Petroleum University, Gandhinagar, Gujarat – 382007, India*

[b] *Discipline of Chemistry, Indian Institute of Technology, Indore; POD-1D, 421, Simrol, Khandwa Road, Indore-453552, India*

[c] *Department of Chemistry, IIT Bombay, Powai, Mumbai 40076.*

[d]*Discipline of Chemistry, Discipline of Metallurgy Engineering and Materials Science (MEMS),* [e]*Discipline of Biosciences and Bio-Medical Engineering (BSBE), Indian Institute of Technology, Indore; POD-1D, 421, Simrol, Khandwa Road, Indore-453552, India*

Contents

Abstracts

Sulfonamides are among the most significant class of organic compounds and key components of a wide array of pharmacophores and agrichemical. These sulphonamides are used as the chemotherapeutic agents against microorganisms. Sulfonamides possess broad spectrum pharmacological activities like antibacterial, antifungal, antiprotozoal, antiretroviral, antihypertensive and antiretroviral activity. However, due to antimicrobial resistance (AMR) has resulted in universal demand for the new generation of sulfonamide derivatives. These sulfonamides primarily inhibit multiplication of bacteria by inhibiting the folic acid synthesis.

As a consequence of this scenario, several homogeneous and heterogeneous transition metal complexes have been developed for the facile synthesis of these sulfonamides. Amongst all, copper-based homogeneous and heterogeneous catalytic materials have been extensively investigated to synthesize a variety of sulfonamides due to the presence of multiple oxidation states, facile electron transfer and ability to complex with a variety of organic moieties. These copper-based catalytic systems effectively catalyze the sulfonylation of organic compounds by direct C-H functionalization of various organic molecules or by multicomponent domino reaction of various organic molecules amines, carbonyl compounds, silanes, with sulfur dioxide, sulfonyl azides or tosylamines. Herein, the present review we focus on the recent developments in the copper catalysed synthesis of sulfonamides and their biological implications.

1. Introduction

Sulfonamides are versatile, functional group chemicals finding applications in a variety of present-day anti-microbial drugs, pharmaceuticals, agrochemicals and medicinal chemistry. Sulfonamides exhibit bactiriostatic activity against the gram postivie and gram negative bactria like *Salmonella Nocardia*, *Klebsiella*, *E. Coli*, *Shigella* and *Enterobacter*. These sulfonamide's functionality is key constituents of a wide array of biologically active compounds like anti-inflammatory, anticancer, antifungal, antiprotozoal, anti-tumor, anti-HIV protease inhibitor, hypoglycemic protease inhibitors, anticonvulsant, antidiabetic agents, antimicrobial and protease inhibitory activity.[1] Moreover, sulfonamides are also effective in the treatment of rheumatoid arthritis, urinary, intestinal and ophthalmic infections.[2] Apart from the pharmaceutical industries, sulfonamides are key components of agrochemicals in a variety of pesticides like halosafen, sulfentrazone, asulam, oryzalin, fomesafen, etc. [3]Sulfonamides have general formula R-SO_2NH_2/R-SO_2NHR, in which the functional group is directly bound to a variety of aliphatic, aromatic, heterocyclic or sugar scaffolds. The prime reason behind the success of these pharmacophores the unique structure of –SO_2NH- assisting the formation of multiple interactions with DNA or RNA molecules, amino acid residues present in various biomolecules.

Sulfonamides derived drugs till date include sulfisoxazoles, sulfadizine, sulfamethazine, sulfadimethoxine, sulfanilamides, sulfasalazine, etc. Sulfonamides composed of heterocyclic rings like oxazoles (sulfisoxazole), benzimidazoles, thiazoles (sulfathiazole), pyridazine (sulfachlorpyridazine) and quinazolinones exhibit excellet antibactial and activity against both gram positive and gram negative bactrias. N-heterocycles like benzoxazole, benzthizoles, benzimidazoles, pyrimidies and triazole derivatives possess antimicrobial, antibacterial, antifungal, anticancer and antiinfamatory properties.[4] Benzathiazole ferivative drug riluzole is used for the treatment of prostrate cancer and brain diesases. Benzimidazole derivatives exhibit anticancer activity. Amidines and bisamidines are important motifs for the treatment exhibit antiprotozolal, antiinflamatory, antiparacitic properties. [5] [6] [7] [8] [9] Recently, sulfonamides containing N-containing heterocycles are very important pharmacophores due to their drung like properties. N-containing hetrocycles like sulfamethazine (SMZ) and sulfadizine (SDZ) are important antibiotic compounds. SDZ possess antibactirial drug used to

treat the gastointestinal and respiratory tract infection in livestocks and is used for the vetenary applications. [10] [11] Moreover, SDZ can also be used as medication for the treatment of infections caused by burn wounds. SDZ can be suplimented with anti-malaria drug pyrimethamine for treatment of toxoplamosis in mammals. Sulfamethazines are primarly used in animal feed to promote growth in animals.[12] Additionally, these sulfonamides are stable, readily synthesised and biocompatiable. Thesefore, several synthetic variants of these sulfonamides have been prepared.[13-15]

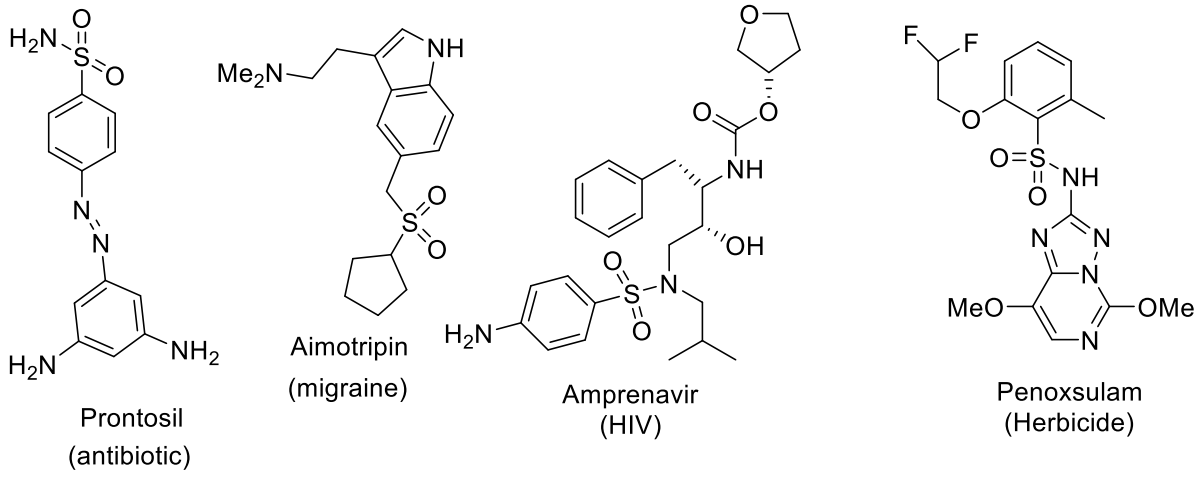


Figure Some important sulfonamides for different biological applications (for details insight see supporting information)

Due to their broad-spectrum applicability, several synthetic techniques have been developed for sulfonamides. Several impressive techniques for the synthesis of sulfonamides like solid-phase synthesis[16], C-H activation[17], metal catalysts[18, 19], flow-based synthesis[20] and metal free synthesis[21] have been invesigated. Broder classification for the transition metal catalysed organic transformation involve (a) transition metal-catalysed; and (b) transition metal free synthesis. Homogeneous and heterogeneous Pd, Ag, Fe, Co, Ni, Cu, Ru and Ir-based transition metal catalysts have been investigated to synthesize aryl sulfonyl compounds. [11] [22] Amongst all, copper-based catalytic systems have received considerable attention for the synthesis of sulfonamides because of their biocompatibility and occurrence in several enzymes catalyzing multiple biochemical reactions. Furthermore, copper (I) catalysts due to readily available variable oxidation states (0 to +3), one or two-electron transfer tendency (similar to palladium), Lewis acid or π-coordination properties impart copper excellent catalytic properties.[23] The synthesis of sulfonamides can be further categorized into two major subclasses. The first class of reactions involves the direct sulfonylation or sulfamidation of a variety of functional groups like saturated C(sp^3)-H bond, olefinic C(sp^2)-H bond, alkyne C(sp)-H bond, amine N-H bond, α, β-unsaturated ketones, alcohols, o-

benzoyl hydroxylamines, aromatic and heteroaromatic compounds. Alternatively, multicomponent domino reactions have also been investigated for the sulfonamides by reacting a vary of substrates like amines, aldehydes or alkynes with sulfur dioxide or an organic molecule containing sulfonyl moiety. In the present work we have revied recent develpments in the application of homogeneous and heterogeneous copper catalysts as the earth-abundant, economical and robust catalyst for the sulfonamide synthesis.

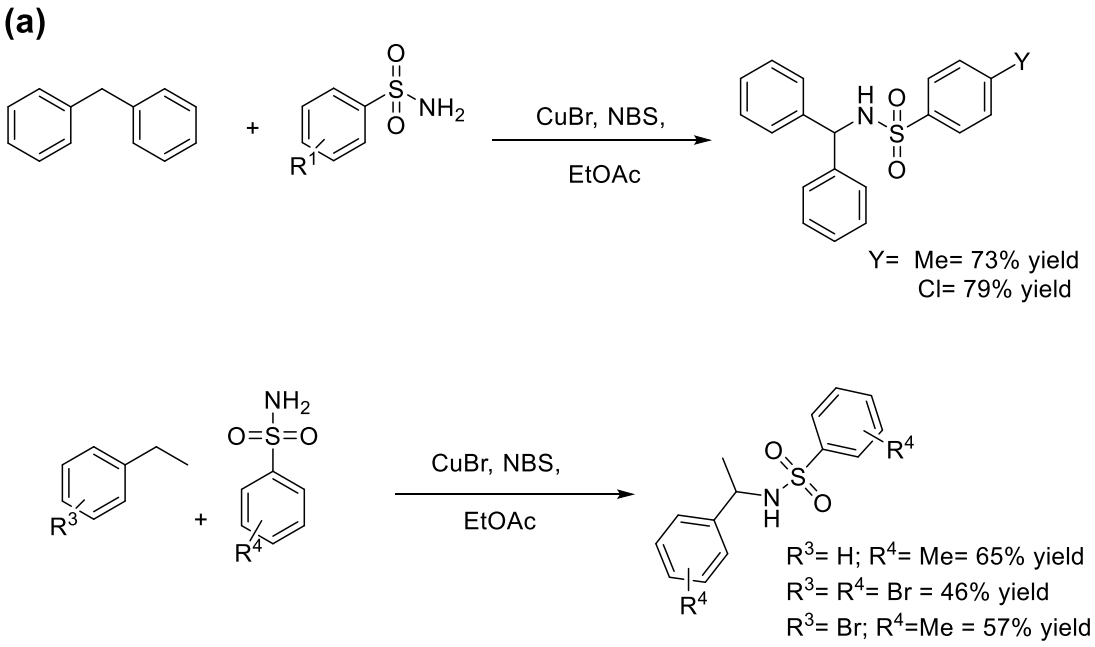
2. Copper-catalyzed amidation reaction

Copper-based homogeneous and heterogeneous catalysts have been extensivey investigated for the sulfonamide synthesis via direct C-H, O-H, N-H/N-X and S-H bond activation. Altrnatively, copper based catalysts have also been invesitgated for the multicomponent domino reactions.

2.1. Sulfonanide synthesis by direct C-H activation

2.1.1. Sulfonamides synthesis from C(sp^3)-H bond activation

CuBr/*N*-halosuccinimide (NBS or NCS) promotes the amidation of saturated C(sp^3)-H under moderate reaction conditions to form the corresponding amides via C-H bond activation. The catalytic system transformed a variety of benzylic C(sp^3)-H bonds to the corresponding amides or sulfonamides with moderate to excellent yields with readily available oxidants. Mechanism for the copper catalyzed sulforamide synthesis involves N-H bond bromination using NBS followed by reaction with CuBr (**8**) to form intermediate **3**. In the subsequent step intermediate **3** reacts with HBr to form intermediate **4**. The intermediate **4** reacts with **5** to form intermedate **6**. In the final step intermediate **6** undergoes intramolecular rearragement followed by elimination of CuBr and generation of final product **7** (Figure3).[24]



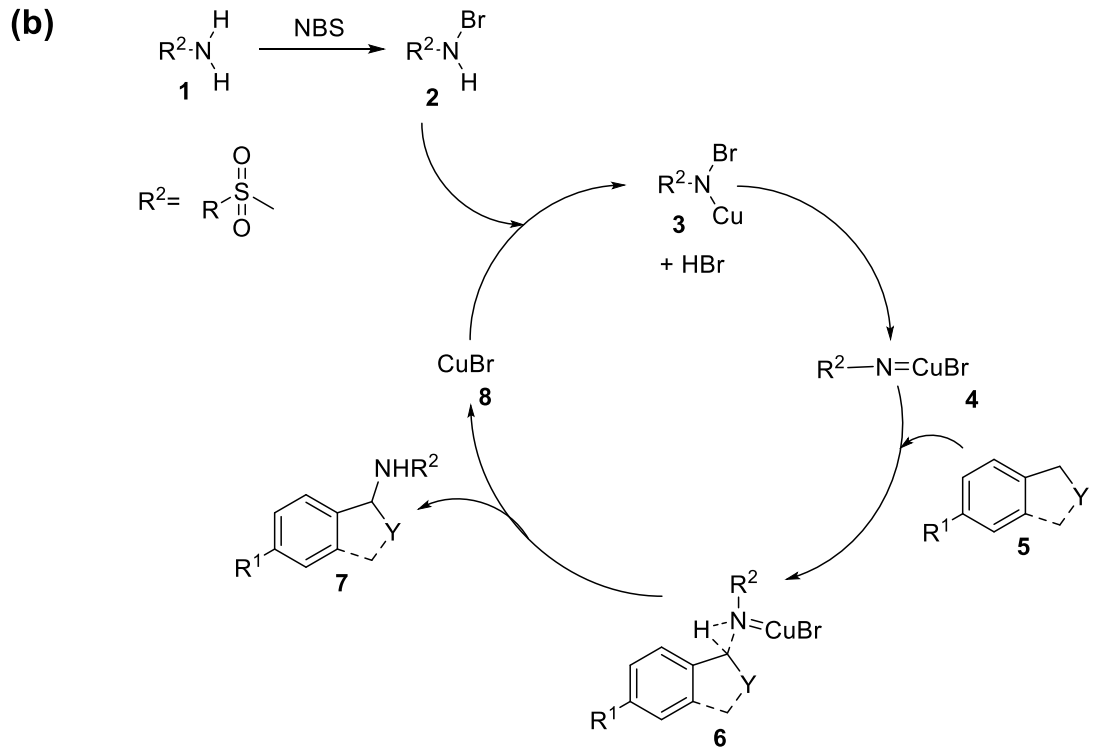


Figure 3.(a) CuBr/*N*-halosuccinimide (NBS or NCS) promotes synthesis of amides and sulfonamides using N-halosuccinamide as an oxidant; (b) Mechanism for the CuBr/NBS catalysed synthesis of sulfonamides

N-sulfonyl enaminone are significant synthetic intermediates finding implication in multistep organic synthesis and their occurrence in diversity of pharmaceuticals and bioactive compounds. However, mostly noble metal based catalysts are involved in the synthesis of *N*-sulfonyl enaminone.[25] CuTC/DMAP has been investigated as the earth-abundant catalyst to promote the synthesis of *N*-sulfonyl enaminone by N-H olefination of sulfonamides. In the reaction system, TEMPO derivatives were used under aerobic conditions using DMSO as a solvent at 110 °C for enaminones synthesis in good yields (Figure 4).[26]

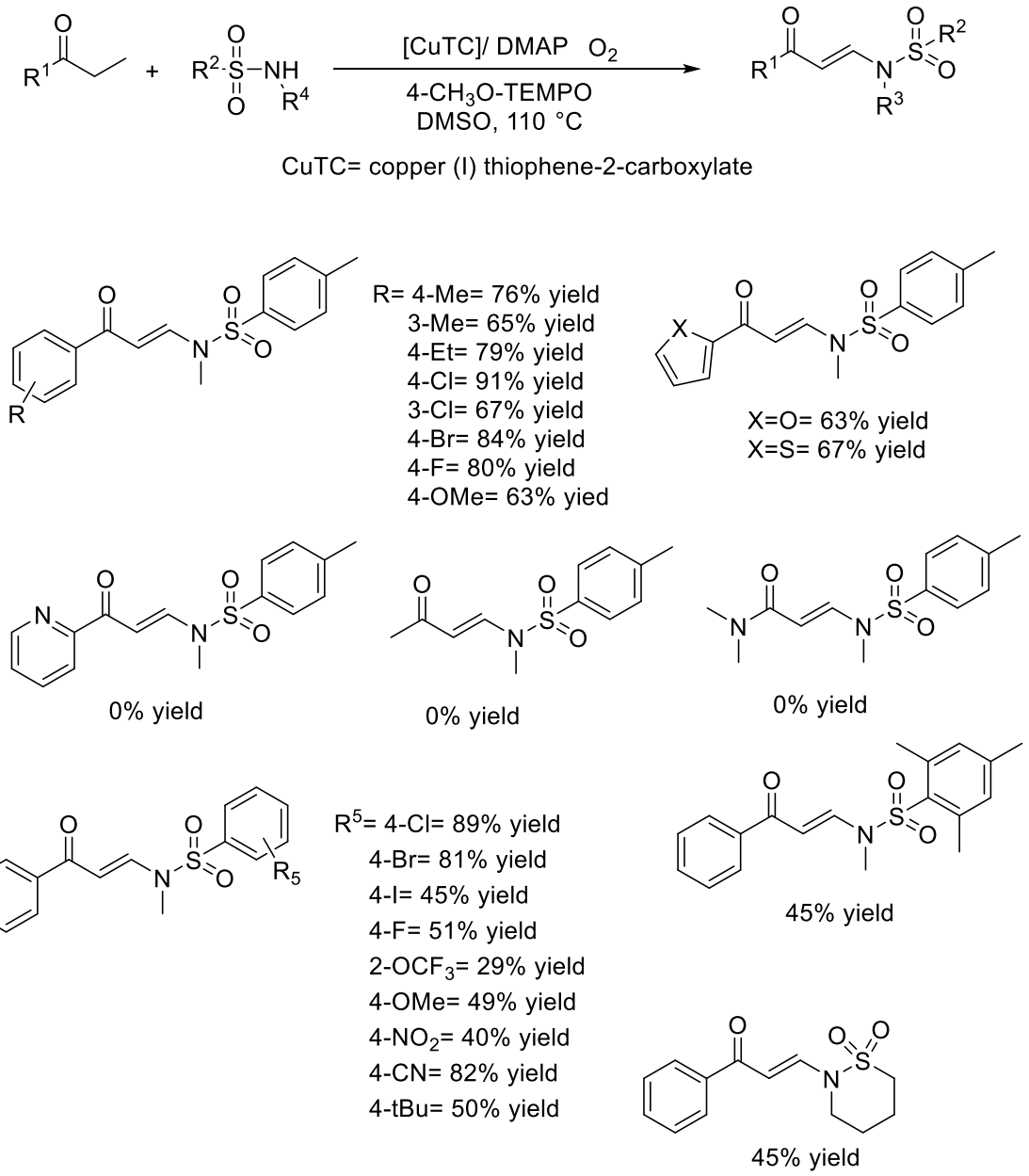


Figure 4. CuTC/DMAP effectively promoted synthesis of *N*-sulfonyl enaminone via N–H olefination of sulphonamides

Mechanistic studies clearly reveal N-olefination of sulfonamides initiates by the formation of copper-ketonic complexes via deprotonation process to from **A** (See Figure 5). The resulting intermediate **A** produces Cu(I) species as key radical intermediate **B**, followed by capturing of **B** by 4-MeO-TEMPO to form intermediate **C**. Then the intermediate eliminates 4-MeO-TEMPO from **C** to form α, β-unsaturated ketones **D**. The sulfonamide gets transformed to radical species **E** by single electron transfer process. The radical addition process of **E** and **D** leads to the formation of intermediate **F,** followed by the addition of another 4-MeO-TEMPO to form α, β-disubstituted product **G.** In the final step, **G** eliminates 4-MeO-TEMPO to form the final product.

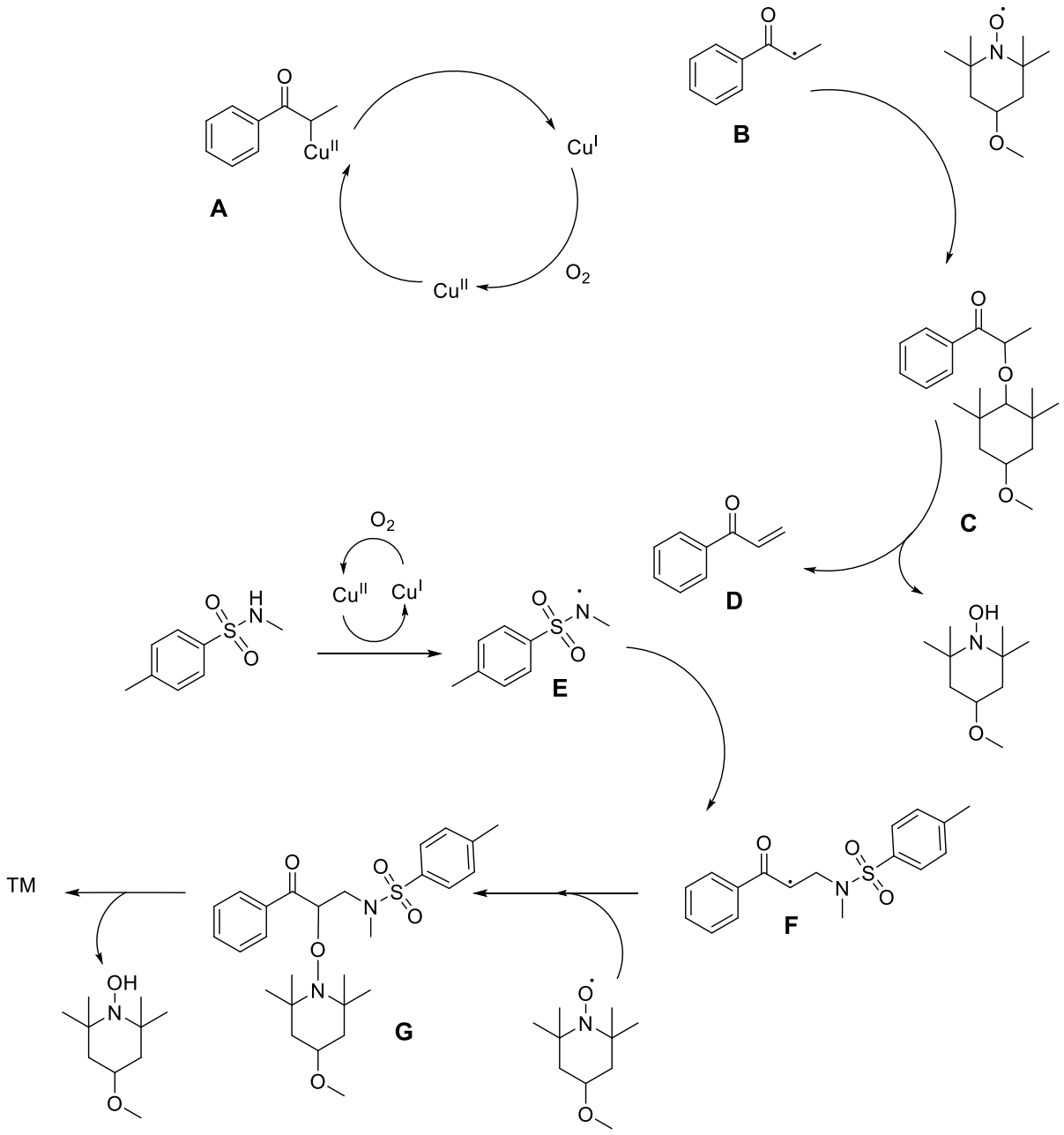


Figure 5. Mechanistic pathway for the copper mediated N-olefination of sulphonamides

Organic compounds possessing isoindoline cores possess medicinal and biological applications like anxitey properties (panzicole) [27], antiretroviral activity [28], lenalidomine for curing multiple myeloma,[29] pestalachloride posses antimicrobial activity.[30] [31] $Cu(OTf)_2/PhI(OAc)_2$ catalyze intramolecular reaction involving sulfamidation at the benzylic methylene resulting in the formation of *N*-arylsulfonyl-1-arylisoindolinones from 2-benzyl-*N*-tosylbenzamides. The reaction was performed using chlorobenzene and acetic acid as a solvent system (5:1) at 120 °C. Mechanistic studies reveal that the rate-determining step involves C–H bond cleavage followed by slow oxidation *via* the copper π-arene intermediate formation (Figure 6).**[32]**

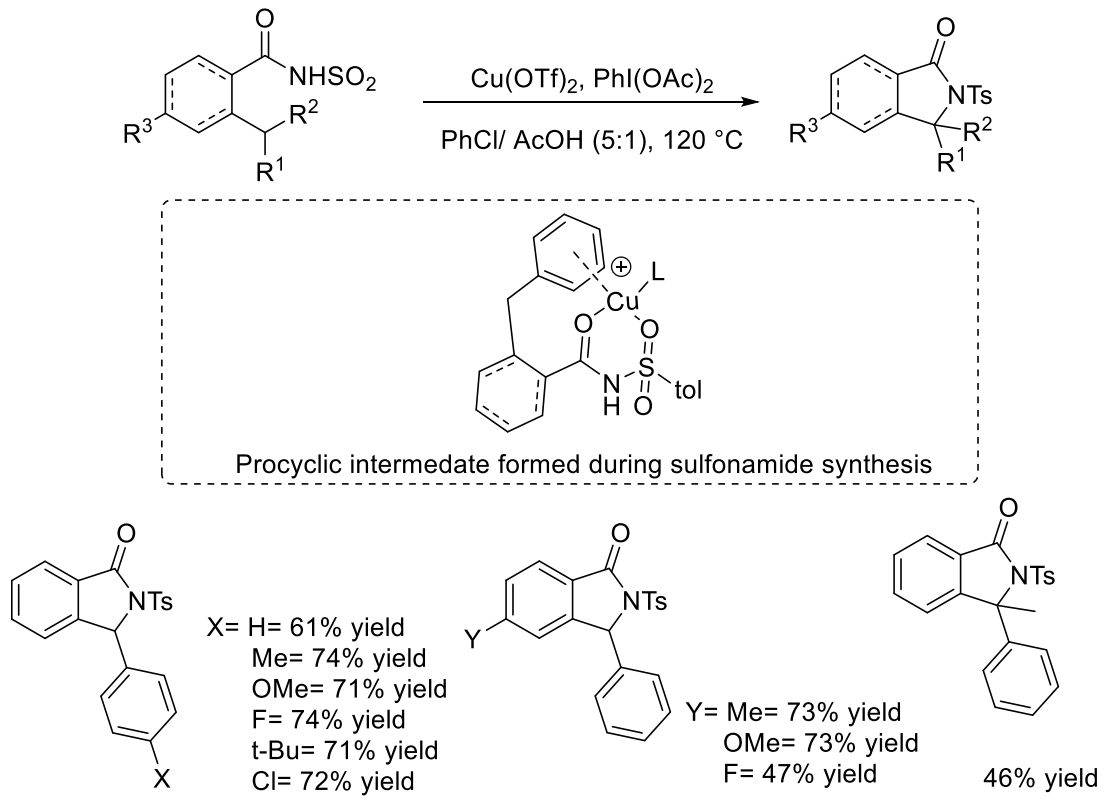


Figure 6 .$Cu(OTf)_2/PhI(OAc)_2$ catalyzed isoindolinones synthesis by intramolecular benzylic C–H sulfamidation

Several organic compounds containing $C(sp^3)$-H bond have transformed to the corresponding sulfonamides using copper catalysts. $[MeCN]_4Cu(I)PF_6$/1,3-indanedione/3-$CF_3C_6H_4COOO$-t-Bu based catalytic system effectively promoted primary benzylic $C(sp^3)$-H amidation with primary and secondary sulfonamides. The reaction system effectively promote the coupling

of the diversity of primary and secondary benzylic hydrocarbons with various sulfonamides (Figure1).[33]

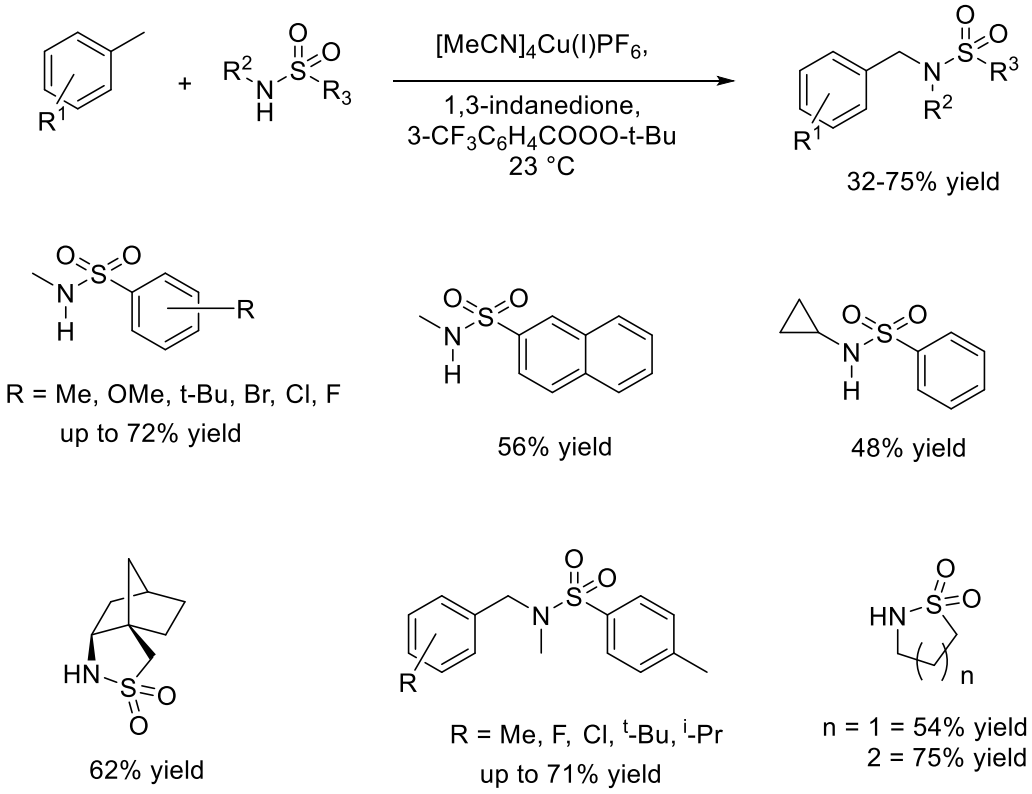


Figure 1. $[MeCN]_4Cu(I)PF_6$/1,3-indanedione/3-$CF_3C_6H_4COOO$-t-Bu catalyzed primary benzylic C(sp^3)−H amidation with primary and secondary sulfonamides

Copper(II) triflate [$Cu(OTf)_2$]/1,10-phenanthroline/t-BuOOAc catalyzes allylic and benzylic C−H amidation with primary and secondary sulfonamides under facile reaction conditions. The catalytic system effectively promoted the reaction of various aryl, heteroaryl, and alkyl sulfonamides to afford a variety of N-alkylated amides (Figure 2).[34]

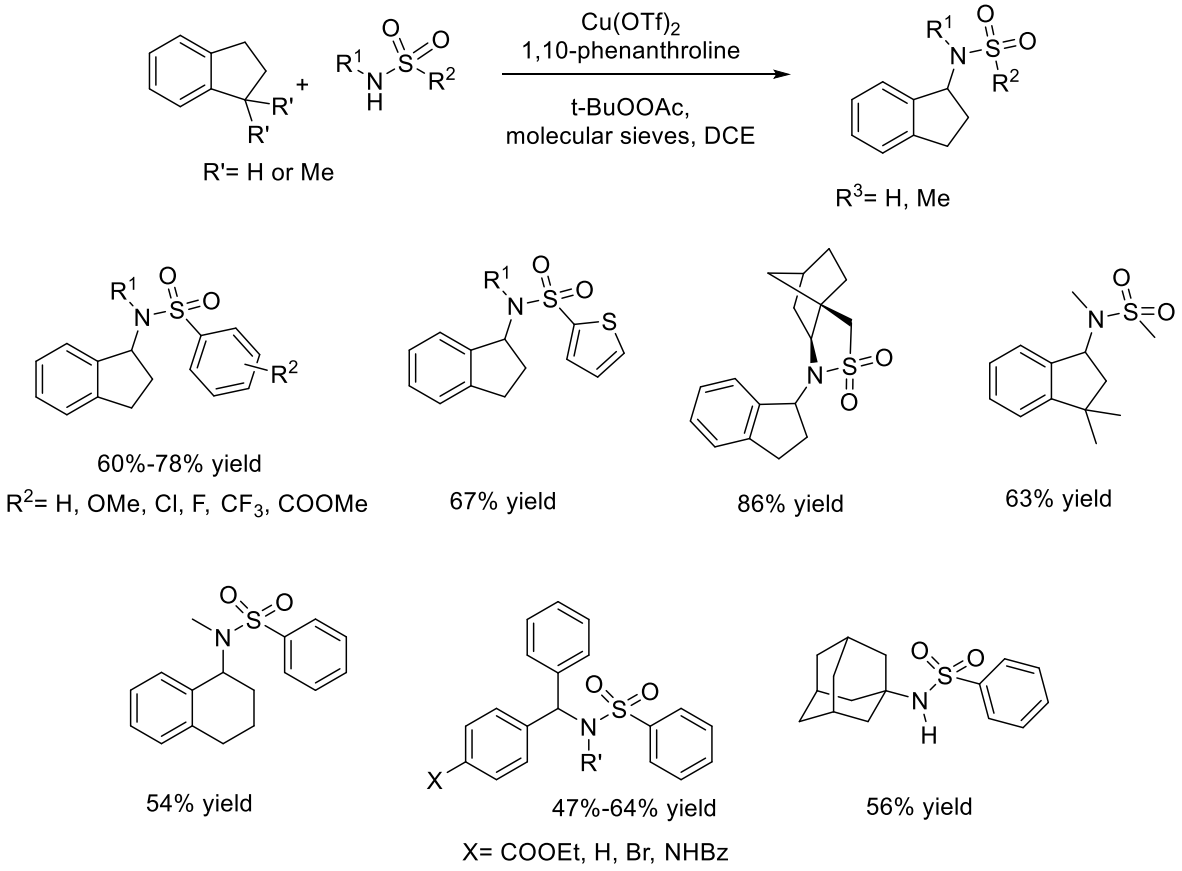


Figure 2. Copper(II)triflate [$Cu(OTf)_2$]/1,10-phenanthroline/t-BuOOAc catalyzed addition of allylic and benzylic C−H bond

2.2.2. Sulfonamides synthesis by C(sp^2)-H and C(sp)-H bond activation

$Cu(CH_3CN)_4ClO_4/PhI(OAc)_2$ promoted one-pot synthesis of alkene aziridination with sulfonamides using 2,2-bis[2-[(4S)-t-butyl-1,3-oxazolinyl]] propane-based ligand under ambient conditions and benzene as solvent. The catalytic reaction proceeded by using $PhI(OAc)_2$ and sulfonamides, assisting the production of nitrene precursors (PhI=NR) *in situ* olefin aziridination. The catalytic system helped to synthesize asymmetric alkene aziridine in moderate to excellent yields(Figure 7).[35]

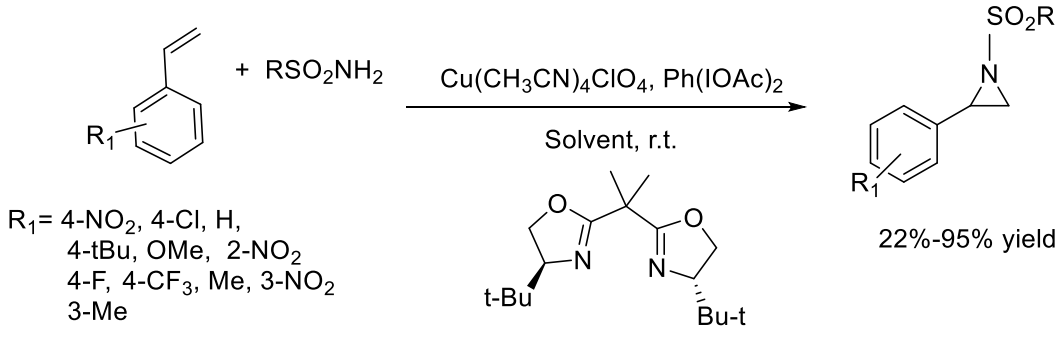


Figure 7. $Cu(CH_3CN)_4ClO_4/PhI(OAc)_2$ was used as an effective catalytic material for alkene aziridination

Heterocyclic 2-aminomethyl indolines and pyrrolidines are favorable organic motifs finding applications in asymmetric catalysis and medicinal chemistry. [36] [37] [Cu(R,R)-Ph-boc]$(OTf)_2$/ MnO_2/ $KMnO_4$ catalyzed highly enantioselective vicinal diamines, including 2-aminomethyl indolines and pyrrolidines, leading to the synthesis of bioactive compounds. The catalytic reaction proceeded by intra-/intermolecular reaction sequence involving γ-alkenyl sulfonamide substrate and amine nucleophile to afford corresponding 2-aminomethyl indolines and pyrrolidines (Figure 8).[38]

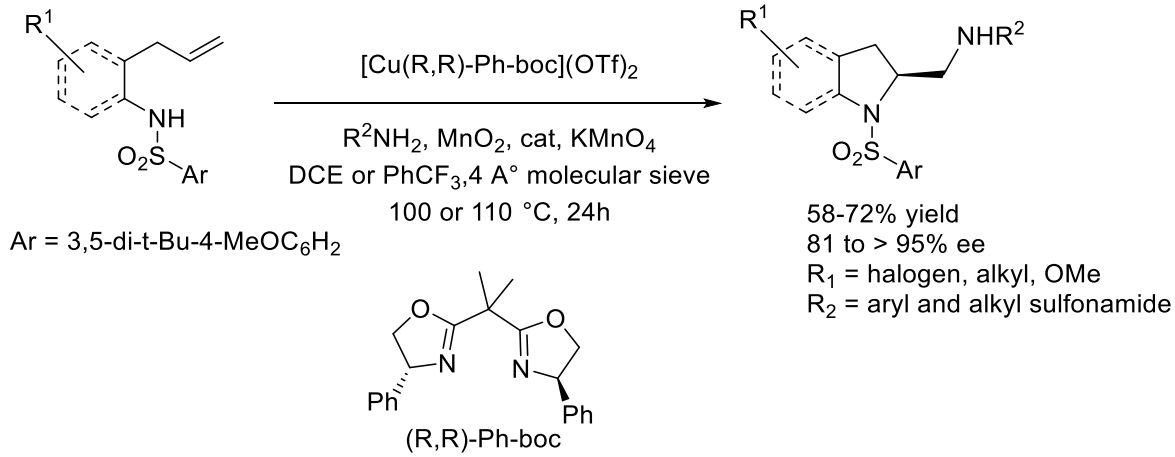


Figure 8. [Cu(R,R)-Ph-boc]$(OTf)_2/MnO_2/KMnO_4$ promotes the synthesis of heterocyclic compounds

Mechanistic pathway for the copper catalysed heterocycle synthesis initiates by the coordinative incersion of γ-unsaturated sulfonamides to Cu(II) ions followed by cis-amino-cuparation reaction leading to the formation of unstable organocopper(II) intermediate. Homolytic cleavege of [C-Cu(II)] results in the formation of primary carbon radical. Mechanistic studies performed using isotopic labelling reveal that the sp^2-hybridized carbon followed by the formation C-N bond and retention of the inversions at the carbon. Addition of the the [copper(II)-NHR] species generated [copper(III)-NHR] species being analogus to the Karash-Sosnovsky reaction. In the subsequent steps vicinal C-N bond formation resulted in the formation of vicinal diamines. The S_N^2 displacement and reductive elimination resulted in the C-N bond formation was favored by reductive elimination of electron-rich amines as compared to electron-poor amine. In the reaction system stoichiometric oxidants like MnO_2 promote Cu(I) to Cu(II) formation (See Figure 9).

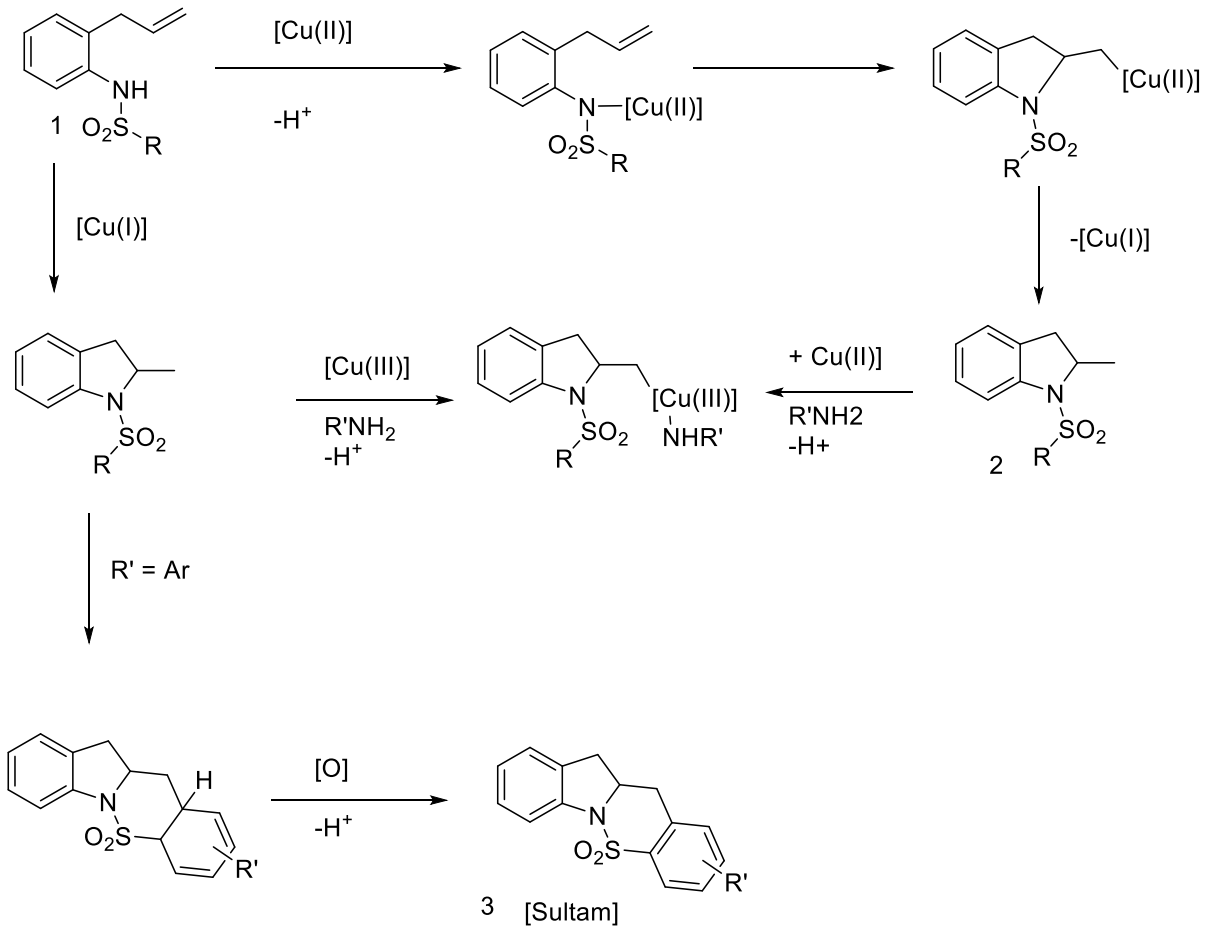
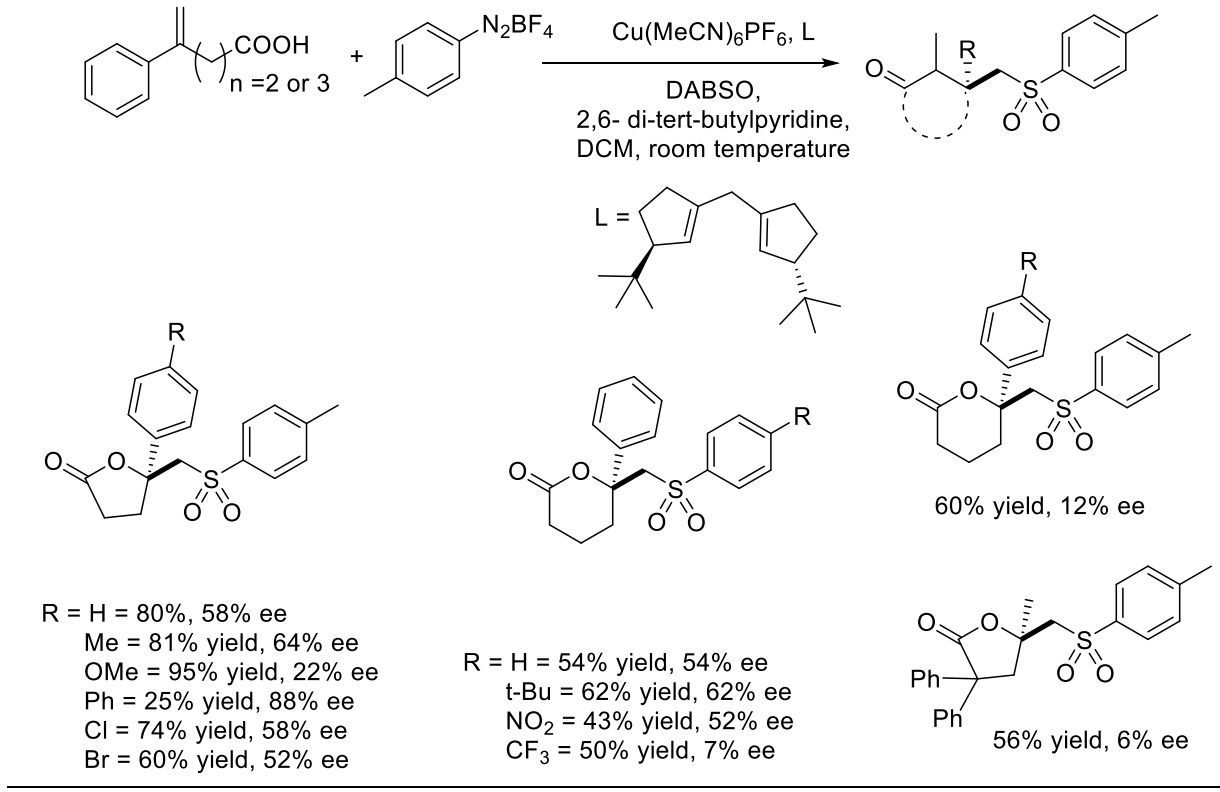


Figure 9. Mechanistic studies for the copper catalysed synthesis of heterocyclic compounds

Chiral sulfonyl lactones are used as valuable chemicals and pharmaceutical compounds. $Cu(MeCN)_6PF_6$ in the presence of chiral ligands effectively catalyzed asymmetric radical-mediated three-component tandem cascade process involving reaction of unsaturated carboxylic acid, aryldiazonium tetrafluoroborate, and $DABCO{\cdot}(SO_2)_2$ (DABSO) to synthesize chiral sulfonyl lactones with high enantioselectivity. The catalytic reaction was performed under moderate reaction conditions, affording synthesis of corresponding sulfonyl lactones with high yields and enantioselectivity (95% yields and 88% ee)(Figure 10). The most plausble mechanism for the synthesis of chiral sulfonyl lactones initiates with the Cu(1)-L mediated activation of **7** to form **8** via single electron transfer reaction and generation of Cu(II) intermediate species. In the subequent step DABSO trapped **8** to form **9**. Subsequently, Cu(II) in presence of 2,6-di-tert-butylpyridine base reacts with **2** to form **3**. In the next step, intermediate **3** reacts with **9** to form intermediate **4**. The intermediate **4** rearranges to form intermediate **5** followed by rearrangement to form final product **6** and releases Cu(I)-L complex.[39]



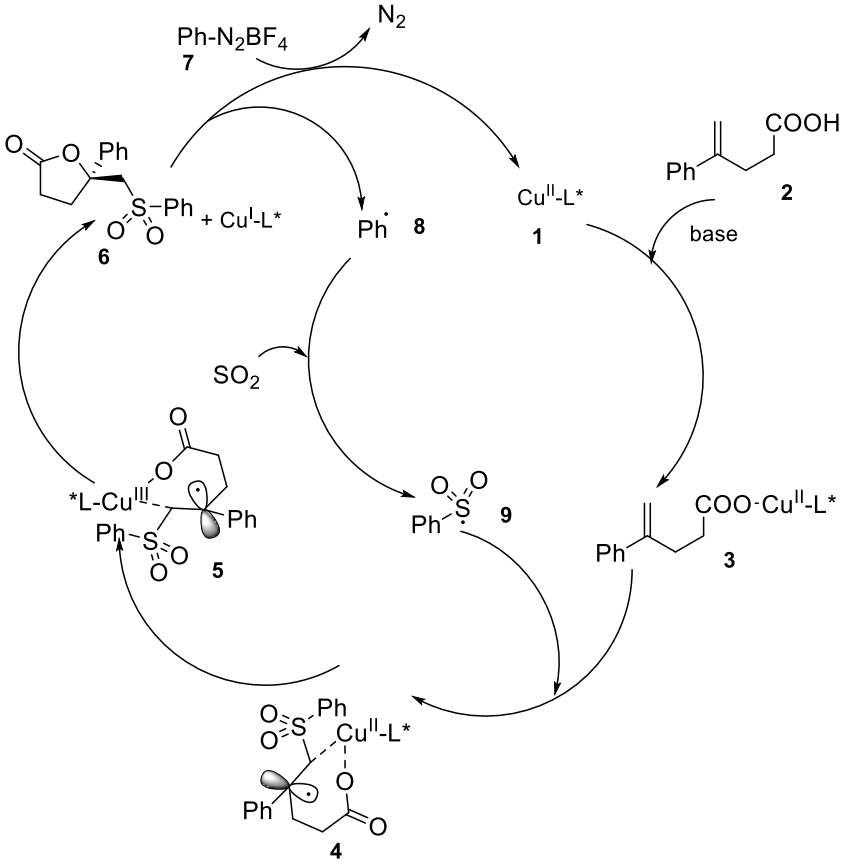


Figure 10. $Cu(MeCN)_6PF_6$ catalyzed the synthesis of chiral sulfonyl lactones via a multicomponent cascade process including mechanism

Cyclic carbonates (sultams) demosntrates broad-spectrum biological applications. For example, oxicams like ampiroxicam are valuable are non-steroidal antinflamatroy agents. Cu(OTf) facilitates synthesis of cyclic sulfonamides from olefinic primary sulfonamides and iodobenzene diacetate. N-alkylated sacchrins are valuable neuroprotactants [40] or anxiolytics (Ipsa-spirone) via acting as the agonists to 5-HT_{1A} receptors.[41] Cyclic sulfonamides selectively inhibit zinc enzme carbonic anhydrase and discovery of antiepileptic agents (sulthiame). Brinzolamine are used for the topical treatment of glucoma (See Figure 11). [42 43]

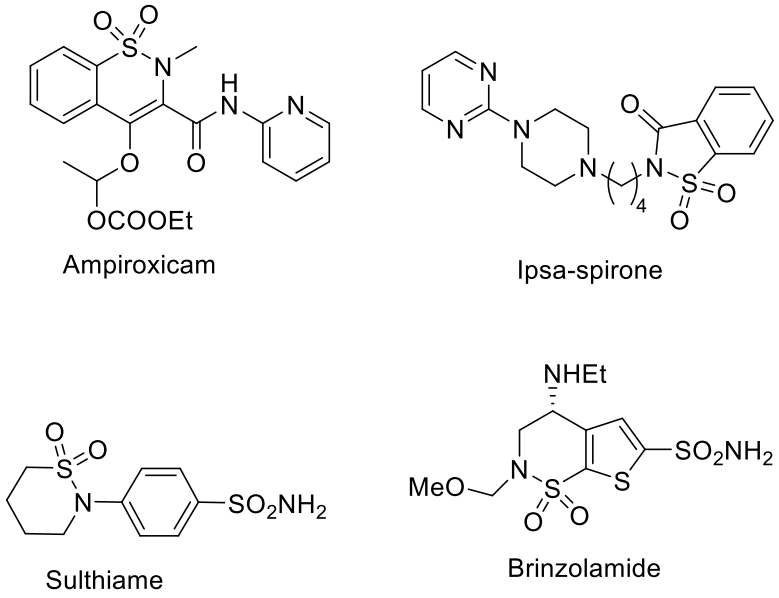


Figure 11. Pharmaceutical applications of cyclic sulfonamides

The reaction was performed using KOH in methanol and acetonitrile as a solvent. Mechanistic studies reveal that the catalytic copper(I) or (II) triflate catalyzed synthesis of aziridine via intramolecular nitrene delivery followed by ring-opening using various nucleophiles (methanol, thiophenol, allylmagnesium bromide, benzylamine) to form cyclic sulfonamides (Figure 11).**[41]**

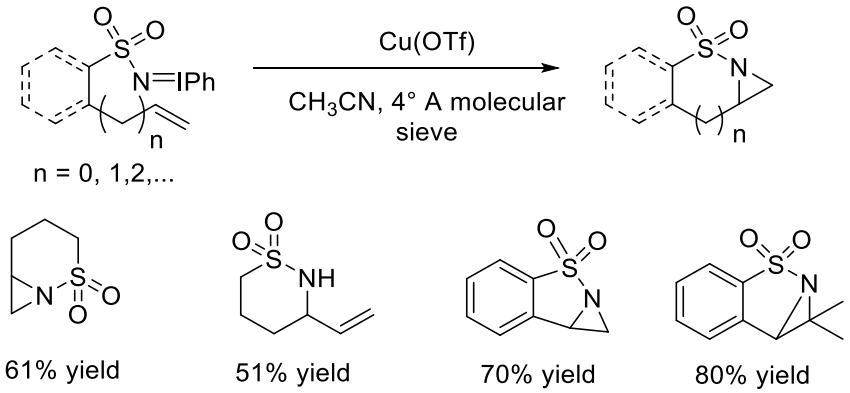
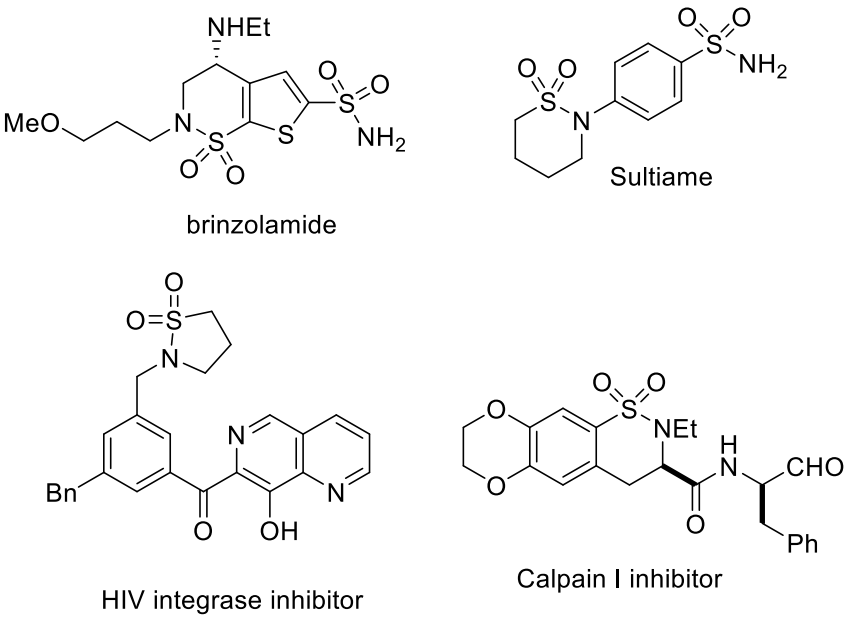


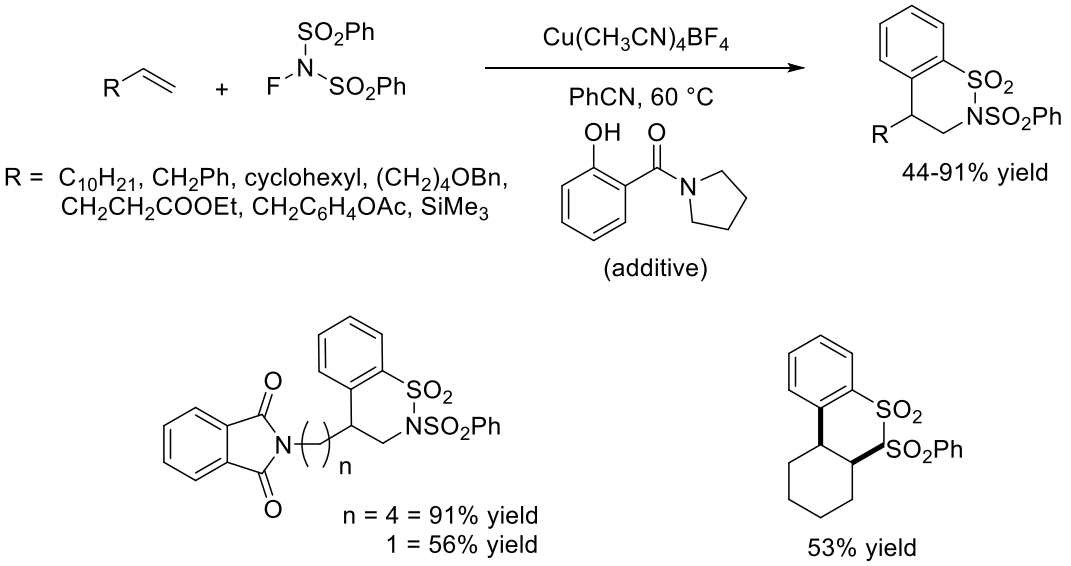
Figure 11. Cu(OTf) catalyzed the synthesis of cyclic sulfonamides from olefinic primary sulfonamides and iodobenzene

$Cu(CH_3CN)_4BF_4$ promotes sultams synthesis from olefins and N-fluorobenzenesulfonamides under moderate reaction conditions. Sultam is significant structural ingredient that is occurring in a variety of biologically significant compounds. Brinzolamide is an important carbonic anhydrase inhibitor assist in lowering the intraocular pressure. Other important sultam are sultimine an anticonvulsent agent, HIV intigrase inhibior and selective calpain I inhibitor (See Scheme 1). [44 45 46]



Scheme 1. Sutlams for multifarious applications

The copper-based catalytic system in the presence of additive and PhCN effectively promoted alkylation of terminal alkenes and an internal alkene reaction with *N*-fluorobenzenesulfonimide at 60 °C to form six-membered ring sultams with 44-91% yields. The postulated mechanim for the copper catalysed intermolecular carboamination reaction involves oxidation of Cu(I) species to Cu(III) species **1** in the presence of NFSI that exhist in equilibrium with species **2**. In the subsequent step species **2** reacts with alkene to form species **3**. In the species **3**, intramolecular addition with carbon radical with the aromatic ring occurs to form intermediate **4**. The indermediate **4** oxidizes to form intermediate **5** followed by regeration of Cu(I) catalyst (Figure 12).[44]



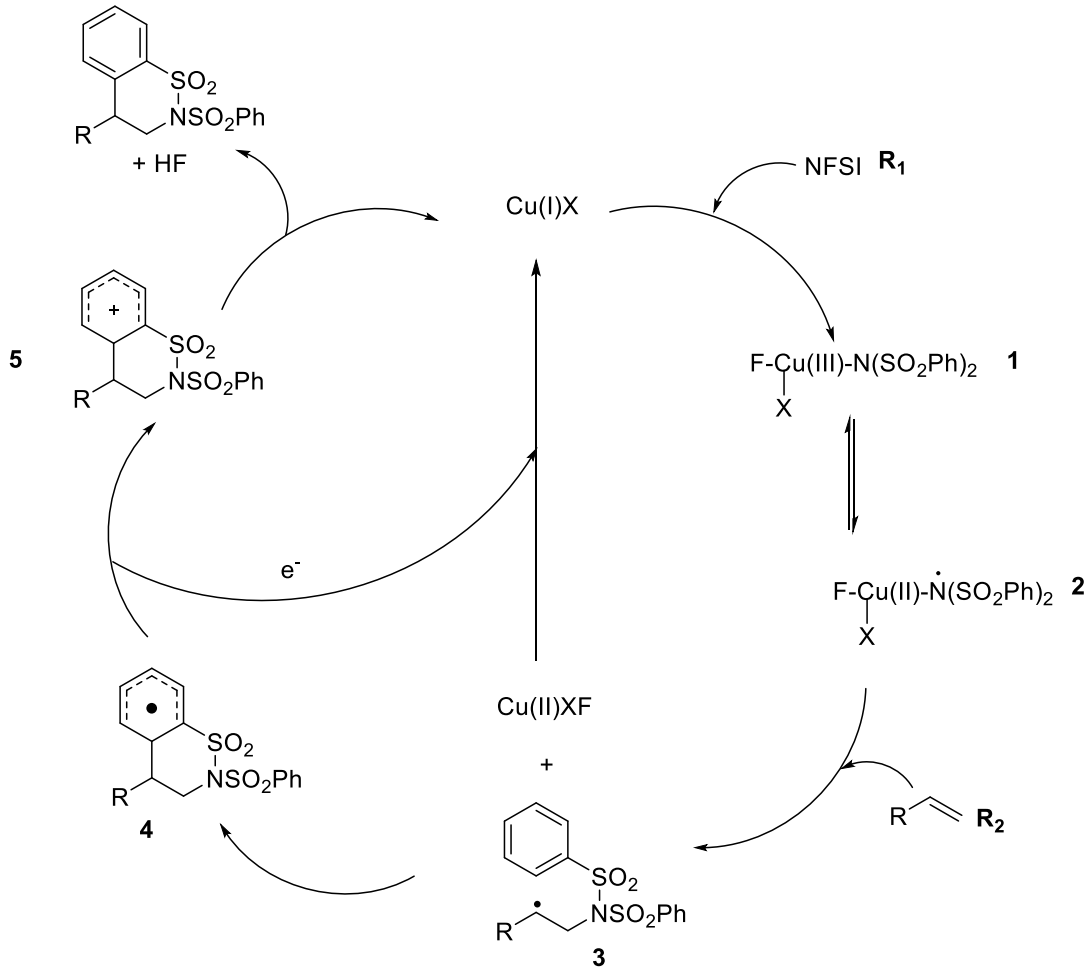
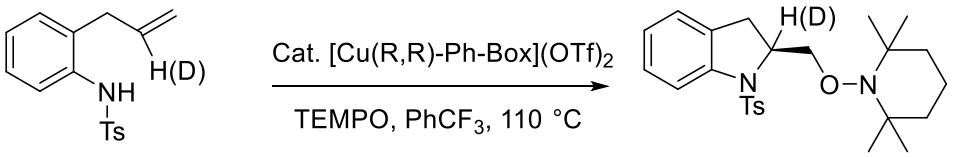
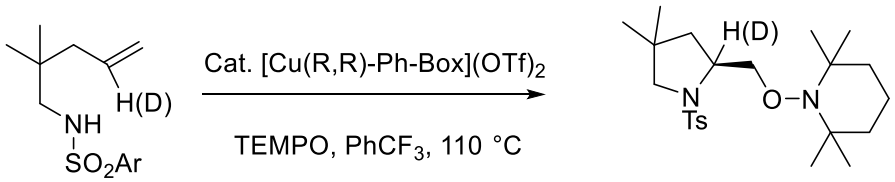


Figure 12. The reaction condition, substrate scope and the mechanism for the $Cu(CH_3CN)_4BF_4$ promoted synthesis of six-membered sultams

The chiral vicinal aminoalcohols are valuable synthetic intermediates, uselful ligands and biological active compounds.[47] [48] [Cu(*R,R*)-Ph-bis(oxazoline)]OTf_2/TEMPO catalyzes asymmetric aminooxygenation of alkenes to form chiral indolines and pyrrolidines in the presence of $PhCF_3$ as a solvent at 110°C. During the reaction the C(4)-phenyl substitution on the bis(oxazoline) assisted in providing excellent asymmetric induction. Furthermore, reaction mechanims was also investigated for the chiral vicinal aminoalcohol synthesis. The mechanistic studies clearly demonstrate that [(R,R)-Ph-Box)Cu](OTf) **1** was the active catalytic species involved in the aminooxygenation reaction via keeping acurate conentration 1:1 between copper and ligand. The catalytic reaction was intiated by the reaction of **1** with the alkene substrate $\mathbf{R_1}$ to form **2**. The intermediate underoges intramolecular rearragement to **3** via the formation of transition state intermdiate **4**. Furthermore, the intermediate **3** undergoes homolytic cleavege to form intermediate **5** and **7**. The intermediate **5** acts as the TEMPO radical trap to form final **6**. The intermediate **7** is further oxidized in the presence of TEMPO to regernate catalyst. (Figure 13 and 14).[49]



R= Ts = 90% yield, 88% ee
Ms= 50% yield, 63% ee
3,5-di-Bu-$C_6H_3SO_2$ = 89% yield, 91% ee
3,5-di-Bu-$MeOC_6H_2SO_2$ = 85% yield, 92% ee



R= Ts = 88% yield, 88% ee
3,5-di-Bu-$C_6H_3SO_2$ = 92% yield, 96% ee
3,5-di-Bu-$MeOC_6H_2SO_2$ = 94% yield, 97% ee

Figure 13. [Cu(*R,R*)-Ph-bis(oxazoline)]OTf_2/TEMPO catalyzed asymmetric aminooxygenation of alkenes

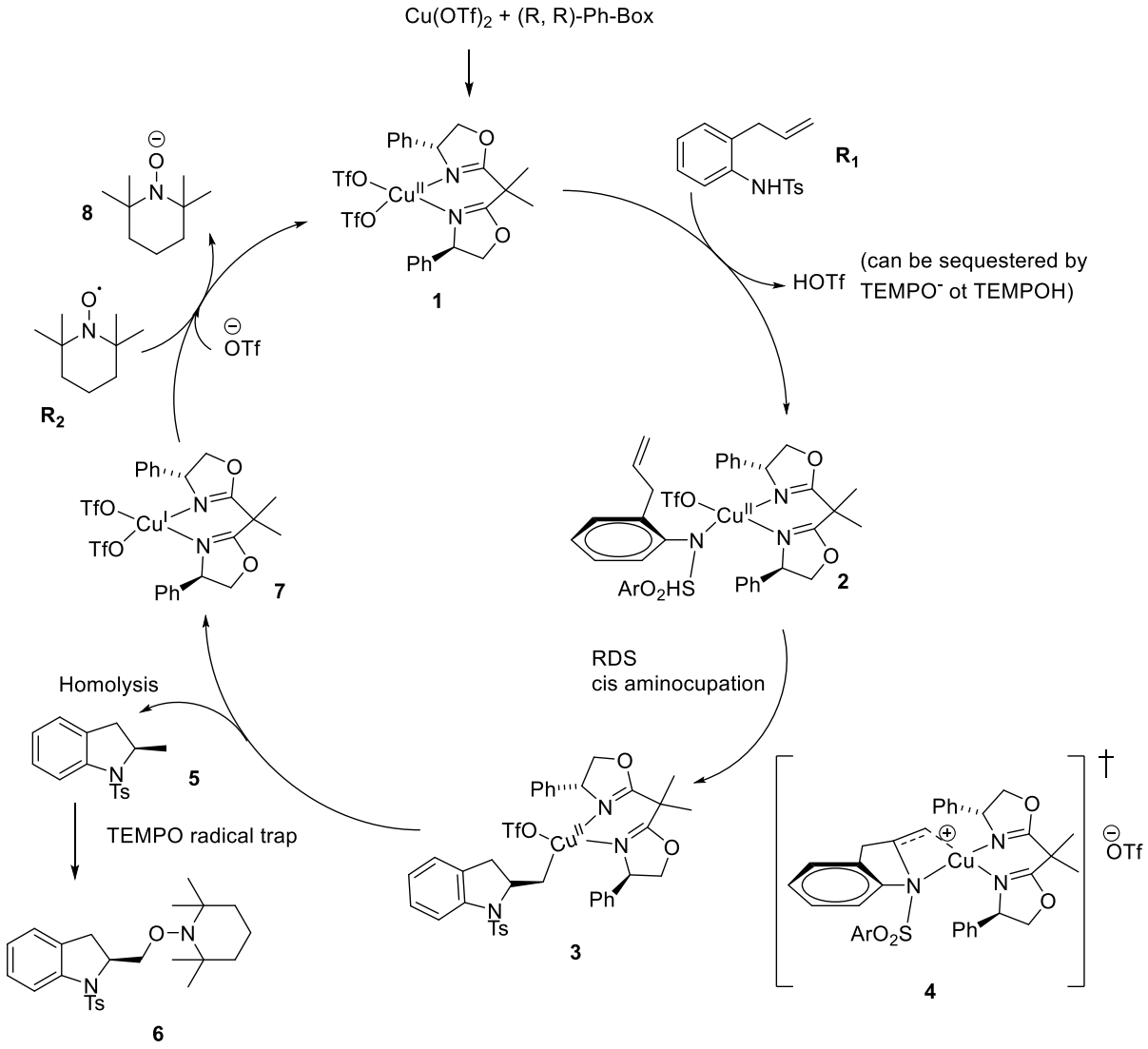


Figure 14. The mechanism for the copper mediated chiral vicinal aminoalcohols synthesis.

N-arylsulfonamides are significant functional scaffolds and biological and medicinal compounds.[50] [51] Copper triflate [$Cu(OTf)_2$]/BINAP catalyzed regioselective additions of arylsulfonamides to vinylarenes, norbornene, and cyclohexadiene under mild reaction conditions. The reaction proceeded by N-H bond addition across the alkenes (the hydroamination reaction). The reaction proceeded in 1,4-dioxane solvent system at 75 °C (Figure 15).[52]

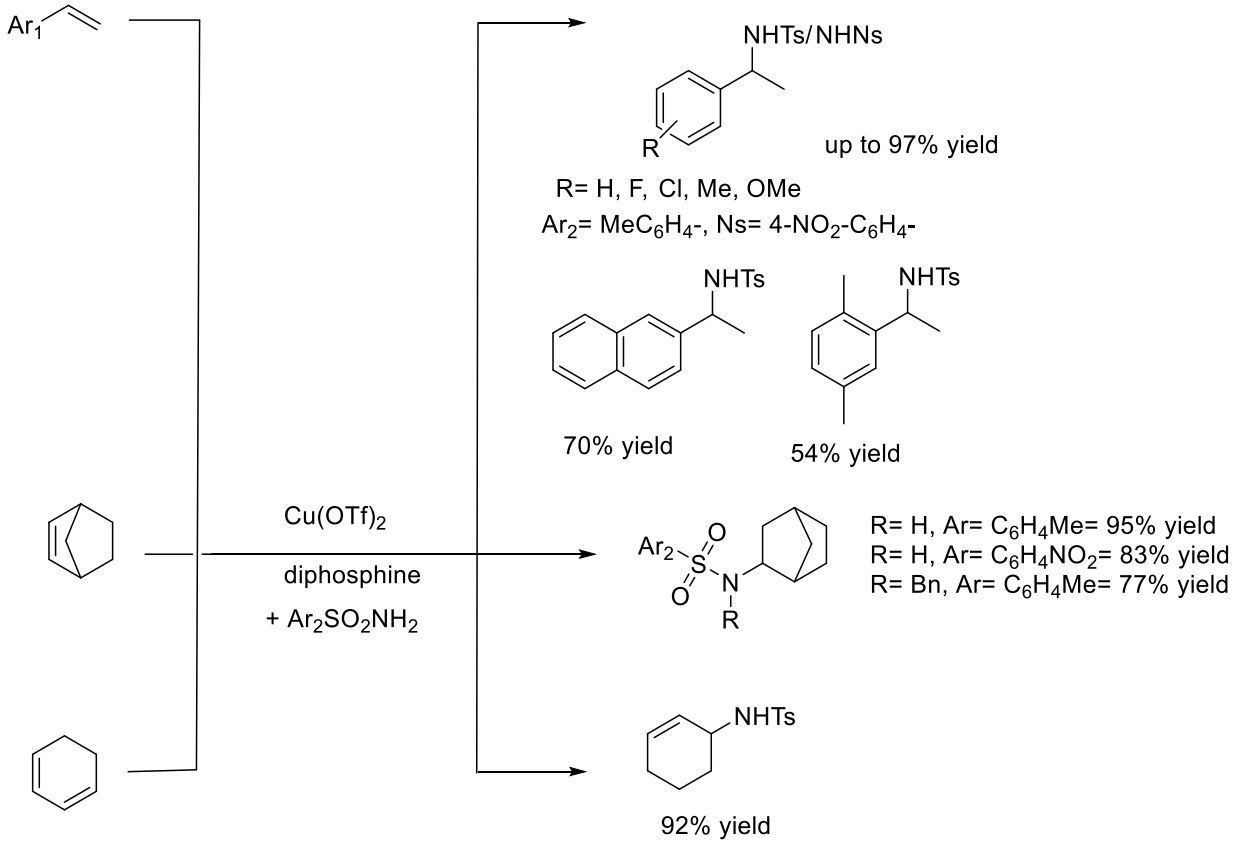


Figure 15. Copper triflate [$Cu(OTf)_2$]/BINAP catalyzes arylsulfonamides addition across C=C bond

Copper(I) chloride catalyzes intermolecular aminoazidation of alkenes to form vicinal amino azides to form important amine derivatives using NFSI as a nitrogen-radical precursor and $TMSN_3$ as the N_3 source. Organic azide are significant organic motifs and building block for bioactive compounds, polymers, material science and valuable pharmacophores. [53 54 55 56] The resulting aminoazide product was obtained in promising yields and diastereoselectivity for internal alkenes. The most plausible mechanism for the intramolecular amino-azidation of alkenes involves reduction of NFSI by Cu(I) species to form Cu(III) species **1** that exisht in equilibrim with N-centerd species **2**. The intermediate species **2** undergos addition with alkene (**1a**) in the presence of Cu(II) species **(3a),** N-radical species **(1b)** and alkene to form species to form intermediate **3 (path a)**. The intermediate **3** reacts with the species **3a** to form intermediate Cu(III) species **4**. In the next step, the intermediate **4** reacts with $TMSN_3$ (**5**) and intermediate **7** and by-product **6**. The intermdiate **7** libreates CuCl to form final product **8** (intermolecular aminoazidation of alkenes). Alternative pathway (**path b**) for the involves reaction between **3** and **3a** to form intermediate **9** and liberation of CuCl. The intermediate 9

reacts with **5** to form final product **8** (intermolecular aminoazidation of alkenes) (Figure 16 and 17). [57].

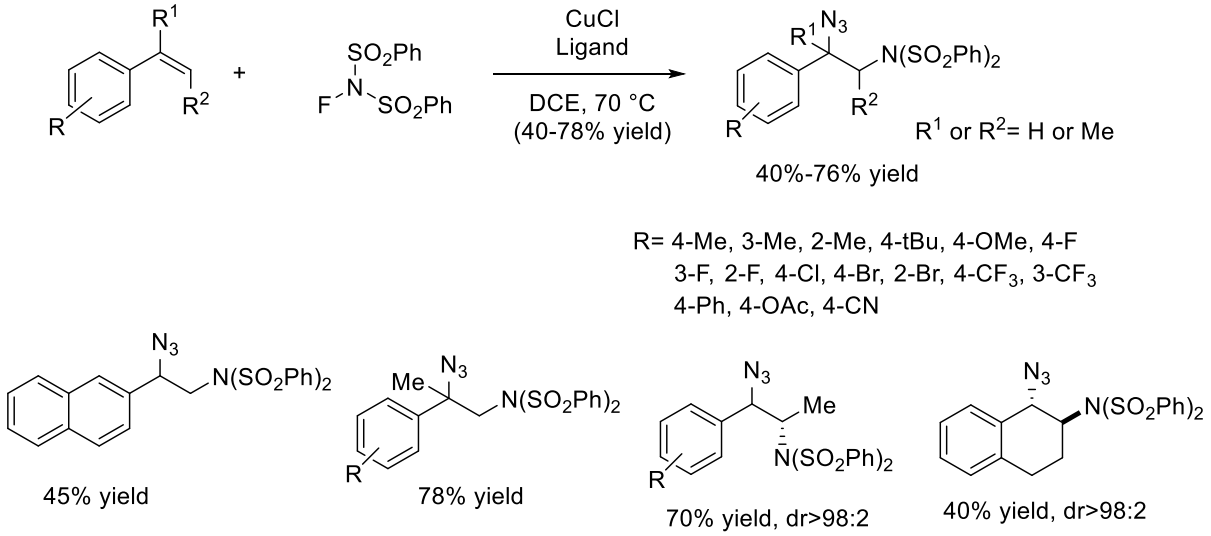


Figure 16. Copper(I) chloride promoted the intermolecular aminoazidation reaction of alkenes to form vicinal amino azides

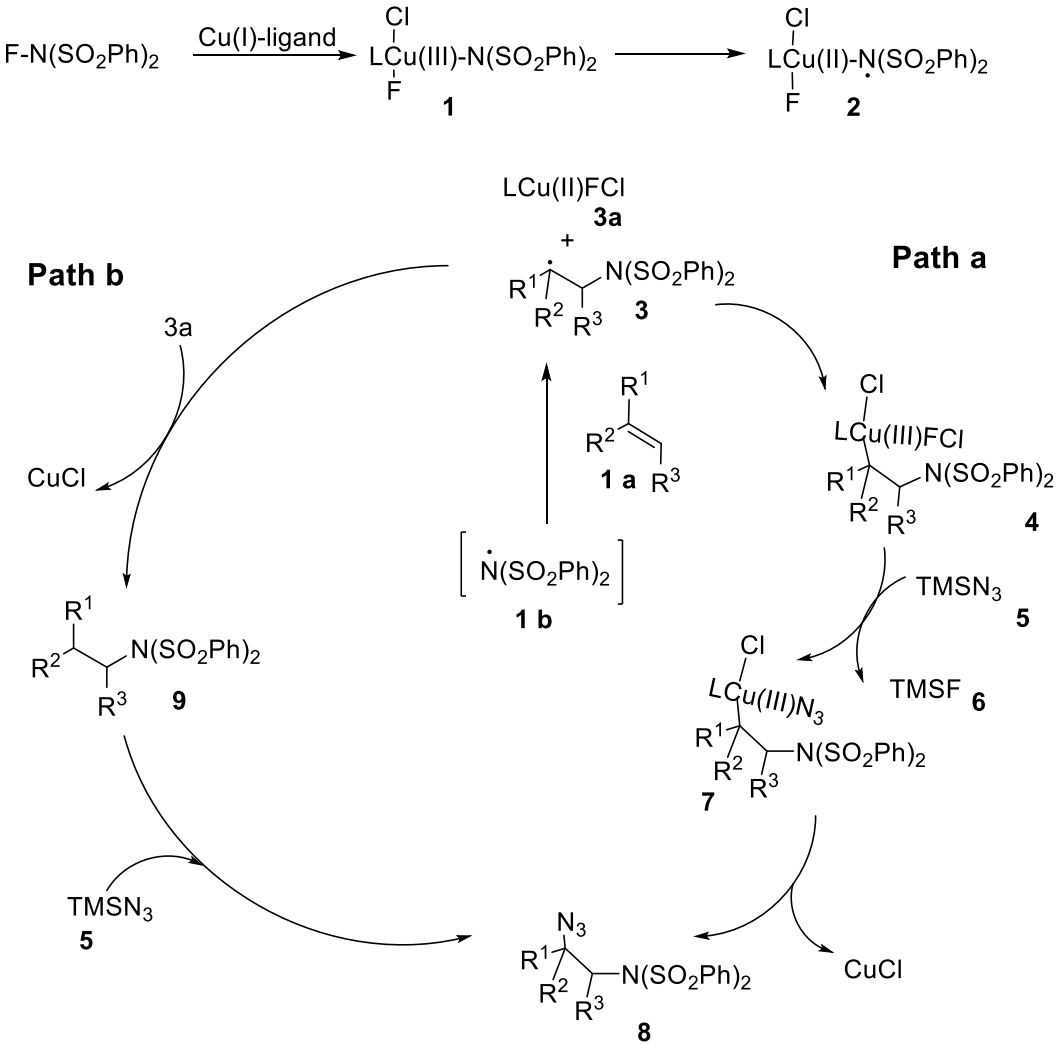


Figure 17. Mechanism for the copper catalyzed intermolecular aminoazidation reaction of alkenes to form vicinal amino azides

Copper(I)bromide/ phenanthroline promotes amino-cyanation reaction of alkenes with NFSI and TMSCN used for the intermolecular diamination of olefinic double bond. The desired amino-cyanation was obtained in good to excellent yield by a facile one-pot process. Furthermore, diamination was performed using NFSI, phenylboronic acid [$PhB(OH)_2$] and aryl or alkyl nitriles in good to excellent yields at 80 °C (Figure 16).[58]

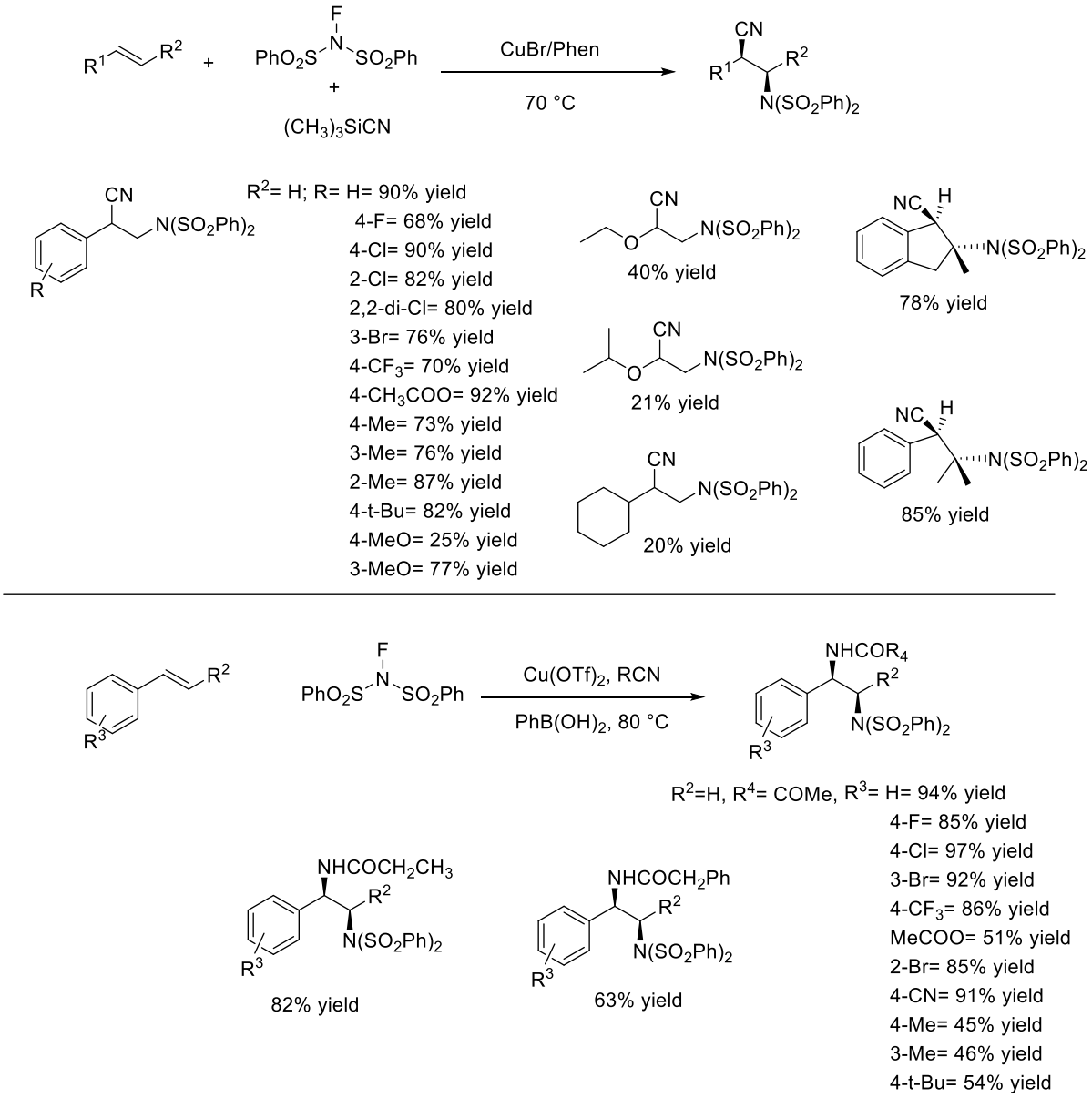


Figure 16. Copper(I)bromide/phenanthroline catalyzes aminocyanation and diamination of olefins

Mechanistic details for the aminoazidation reaction to from vicinal amino azides involves the Cu^{I}, Cu^{II}, Cu^{III} species. The aforementioned catalytic process initiates with the oxidation of CuCl with NFSI leading to Cu^{III} complex with **A** in equilibrium with copper(II)-stabilized benzenesulfonamide radical **B** *via* equilibrium. In the subsequent steps addition of alkene to **B** to the formation of Cu^{II} species **C** and carbon radical intediate **D**. The resuting intermedate **D** combines with **C** to form Cu^{III} species **E** connected via C-Cu bond. The reaction of the intermediate **E** with $PhB(OH)_2$ leads to the formation of intermediate **F**, where $PhB(OH)_2$ supplies the OH moiety. The intermediate **F** interacts with the nitrlies to form intermediate

Cu^{III} complex with **G**. The reductive eleimination of **G** lead to the fomation of final product vicinal amino azide (See Figure 17).

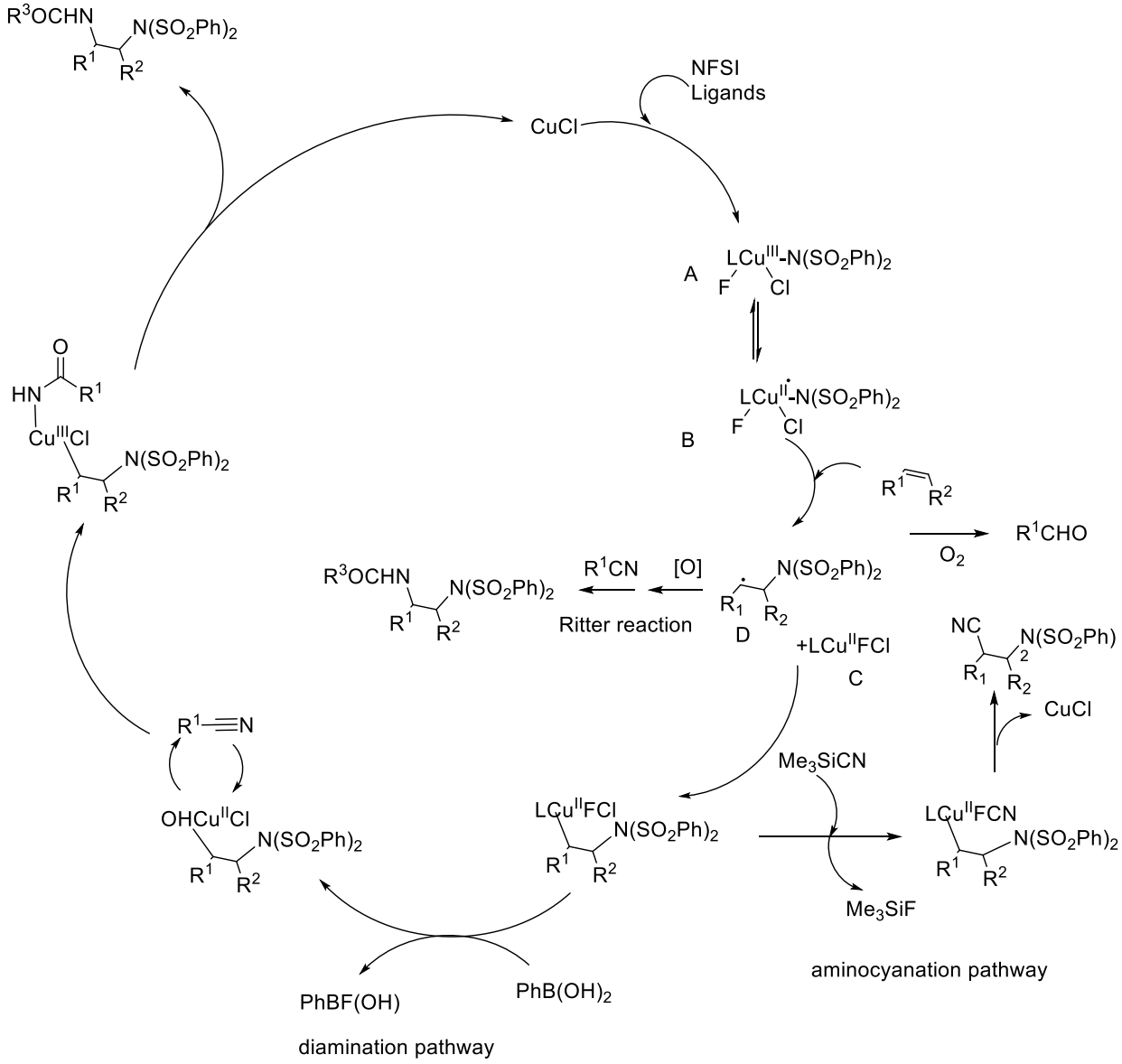


Figure 17. Mechanism for the copper catalysed aminocyanation reaction

Chiral heterocyclic compounds like indolines, pyrrolidines and isoquinolines are significant for organic synthesis and drug discovery. [59] $Cu(OTf)_2/MnO_2/K_2CO_3$ promotes enantioselective Heck-type coupling involving cascade reaction for the synthesis of heterocyclic compounds like chiral indolines, pyrrolidines and an isoquinoline from the respective acyclic γ- and δ-alkenylsulfonamides and vinyl arenes. The catalytic reaction assisted the production of a variety of functionalized heterocyclic compounds in good to excellent yields. Mechanism for the copper catalyzed amination of alkene via Heck type coupling involves the reaction of alkene **1** with copper catalyst **2** to form intermediate species

4. The intermediate species **4** liberated copper catalyst to form intermediate **5**. The intermediate **5** reacts with alkene **6** to form intermediate **7**. The intermediate **7** tranforms to the final product **8** (Figure 18).[59]

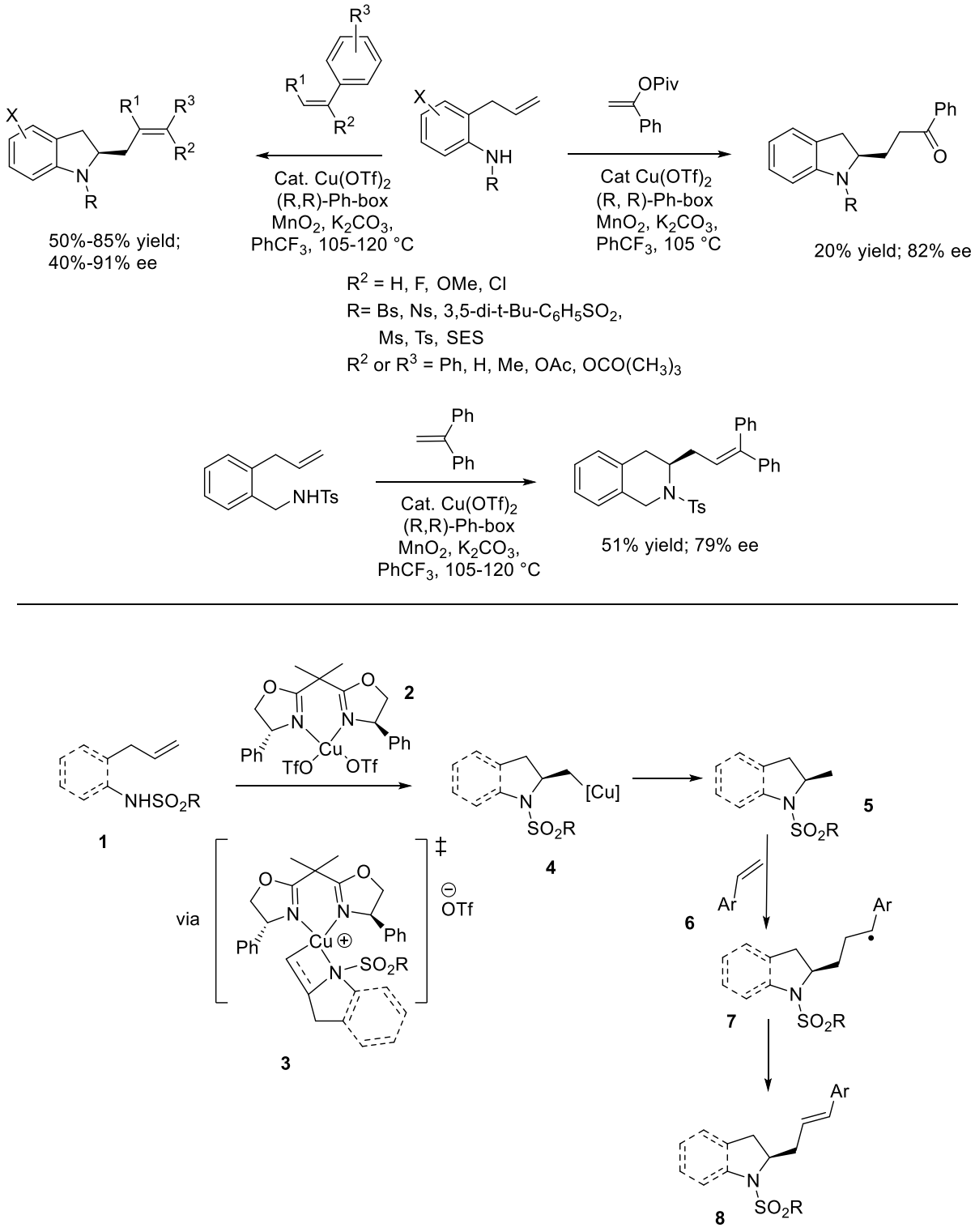


Figure 18. $Cu(OTf)_2/MnO_2/K_2CO_3$ promotes enantioselective synthesis functionalized heterocyclic compounds by intermolecular Heck-type coupling

CuX (X=Cl or I)/pyridine-based catalytic system in the presence of $PhSO_2N$=IPh or $TsNClNA.3H_2O$ (chloramine-T trihydrate) enables amide synthesis by C-H insertion into C-H bond of aldehyde. The aforementioned reaction system affords an economical, easily accessible catalytic material. Mechanism for the copper catalyzed sulfonamides synthesis using aldehydes starts with Cu^+ (**1**) mediated activation of $PhSO_2N$=IPh to form intermedite **2**. The intermediate **2** reacts with aldehydes to form intermediate species **4**. In the final step, intermediate **4** rearrages to form final product (**5**) and regeneration of product. (Figure 19).[60]

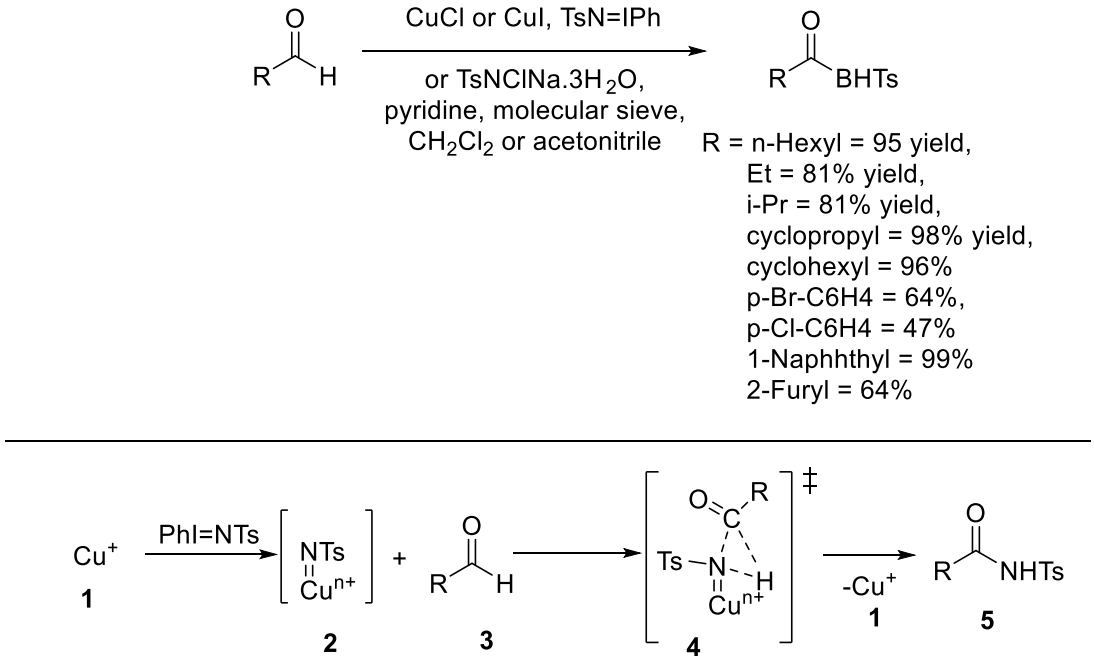


Figure 19. Catalytic application CuX (X=Cl or I)catalyzed aldehyde conversion or C-H amidation using$PhSO_2N$=IPh or $TsNClNA.3H_2O$ (chloramine-T trihydrate)

Copper(I) triflate catalyzes regio- and stereoselective aminohalogenation of cinnamic esters using 2-$NsNCl_2$/2-NsNHNa as nitrogen and chlorine sources. The reaction system provided an efficient method for the synthesis of *anti*-alkyl 3-chloro-2-(*o*-nitrobenzenesulfonamido)-3-phenylpropionate derivatives with satisfactory yields (62−82%) and stereoselectivity [(5:1)−(30:1)]. Mechanism for the copper catalzed sterio- and regio-selective aminohalogenation of cinnamic esters **1** reacts with **2** to form intermediate **3**. The intermediate **3** rearrages to form intermediate **4**. In the final step, intermediate **4** reacts with sodium bicarbonate solution to form final aminohalogenated cinnanic ester **5** (Figure 20).[61]

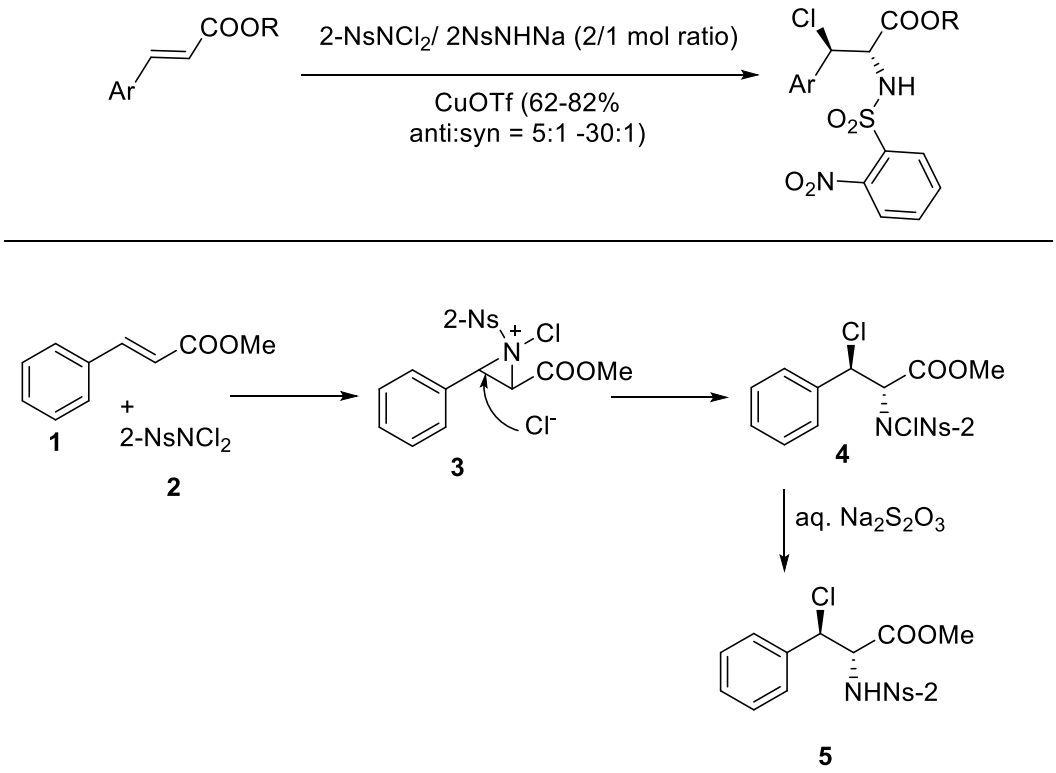


Figure 20. Copper(I)triflate promoted synthesis of *anti*-alkyl 3-chloro-2-(*o*-nitrobenzenesulfonamido)-3-arylpropionates by aminohalogenation using the 2-$NsNCl_2$/2-NsNHNa as nitrogen and halogen sources

α-Amino substituted unsaturated ketone skeletons are a significant class of biologically active enamides. Copper(II)acetate promotes facile synthesis of enamides via oxidative amidation of α,β-unsaturated ketones in the presence of *N*-fluorobenzenesulfonimide (NFSI). The catalytic reaction follows the pathway involving a radical pathway involving the amidation of α-position of the α,β-unsaturated ketones, which subsequently leads to C(CO)–C(vinyl) or C(vinyl)–H bond cleavage (Figure 21). [62]

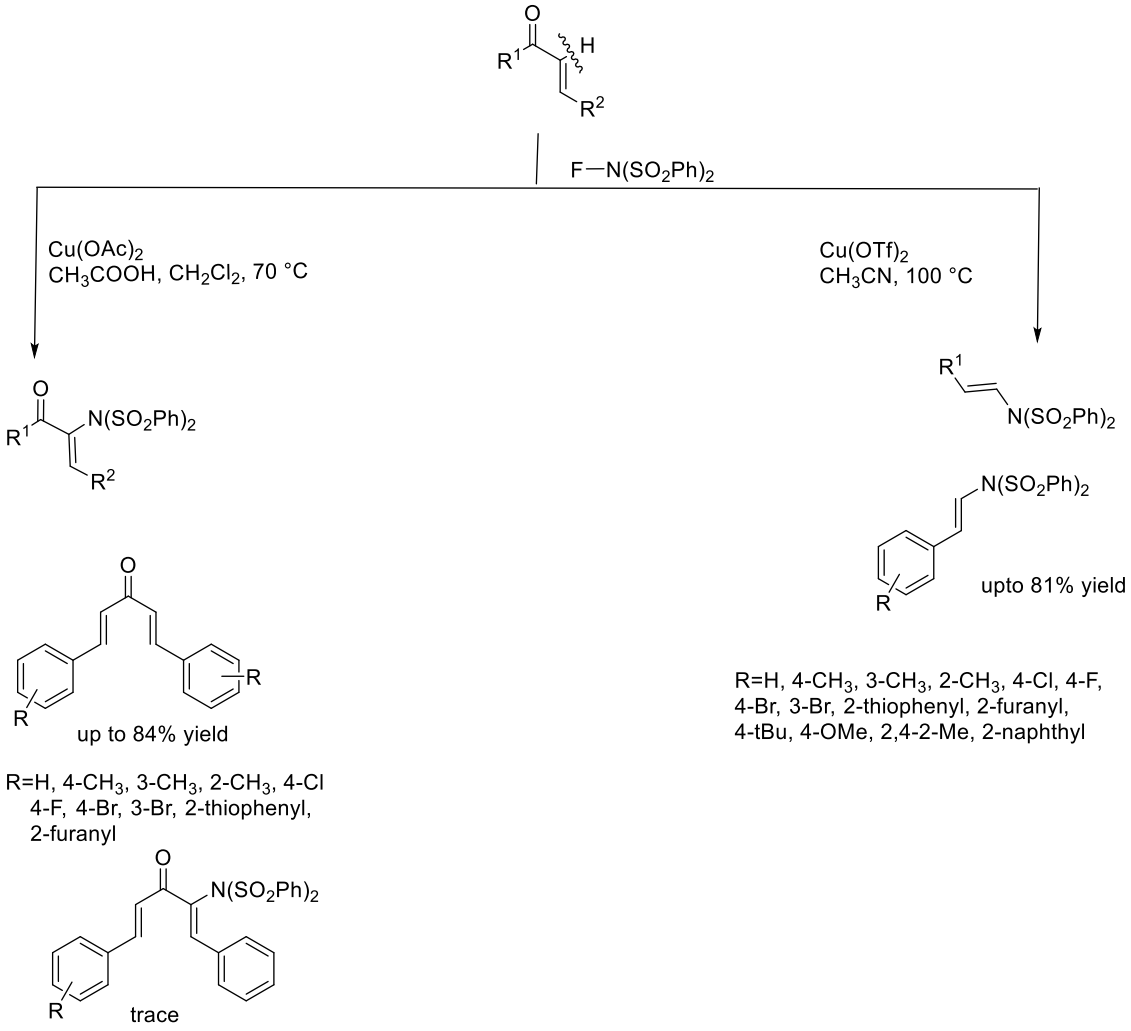


Figure 21. Copper(II)acetate enables amidation of α,β-unsaturated ketones

Mechanism for the copper catalysed amidation of α,β-unsaturated ketones initiates with the activation of NFSI by Cu^{I} species to form Cu^{III}-intermediate **1a**. The intermediate species **1a** undergoes rearragement to nitogen centric species **2**. The intermediate species **2** reacts with [1b] to form intermediate to form radical intermediate **3**. Subsequently, **3** reacts with α,β-unsaturated ketones reacts with NFSI to form final product **P1** and radical intermediate **7**. The radical intermediate **7** reacts with Cu^{II} to regenerate **2**. In the alternative pathway, intermeidate **3** carbon-carbon bond cleavege to form product **P2** and radical intermediate **4**. The radical intermediate **4** reacts with NFSI to form radical intermediate **7**. Finally radical intermediate **7** reacts with Cu^{II} to regenrate **2** (Figure 22).

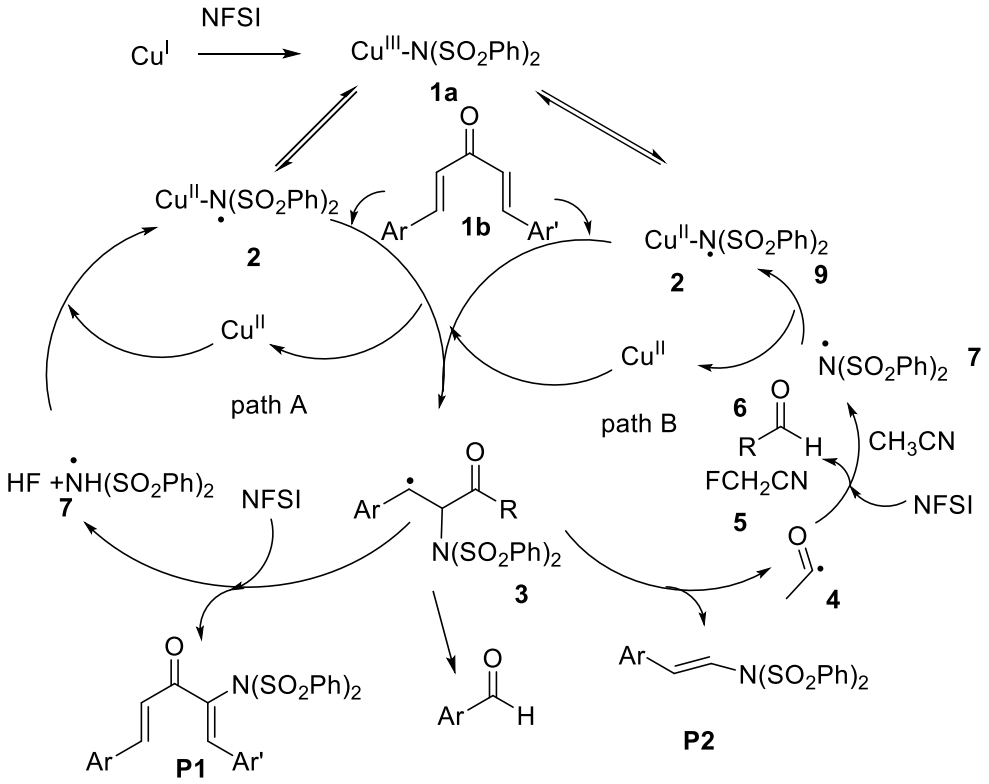
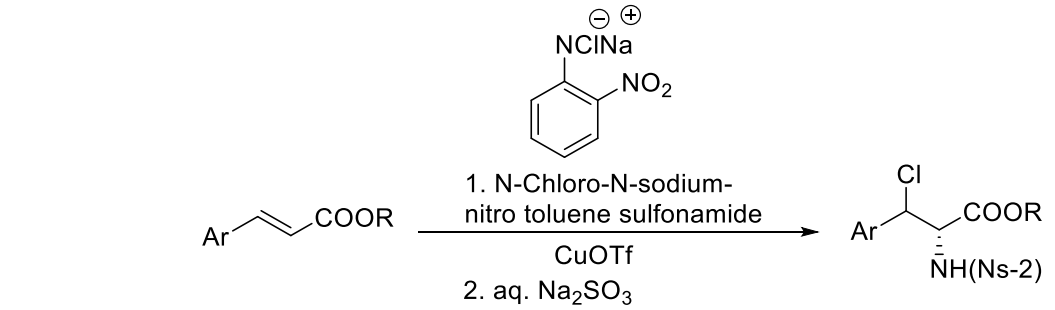


Figure 22. Mechanism for the copper catalyzed amidation of α,β-unsaturated ketones

$Cu(OTf)/Na_2S_2O_3$ was used as the excellent catalytic material for synthesizing vicinal haloamine derivatives *N*-Chloro-*N*-sodium-sulfonamide under ambient conditions. The desired vicinal haloamines were synthesized in excellent regio and stereochemistry. Mechanistic studies reveal that the reaction proceeded by the formation of *N*-chloro-*N*-copper-2-nitrobenzenesulfonyl aziridinium intermediates. The desired aminohalogenated products were prepared with good yields and excellent stereoselectivity. Mechanistic studies for the aminohalogention of olefin with *N*-Chloro-*N*-sodium-sulfonamide **1.** The reaction cycle starts with the reaction of **1** with copper trifalate to form intermediate **2**. In the subesequet step, intermediate **2** reacts with olefin **3** to form intermediate **4**. The intermediate **4** undercoges intramolecular rearragement via intermediates **5** and **6** to form final aminohalogenated product **7** (Figure 23).[63]



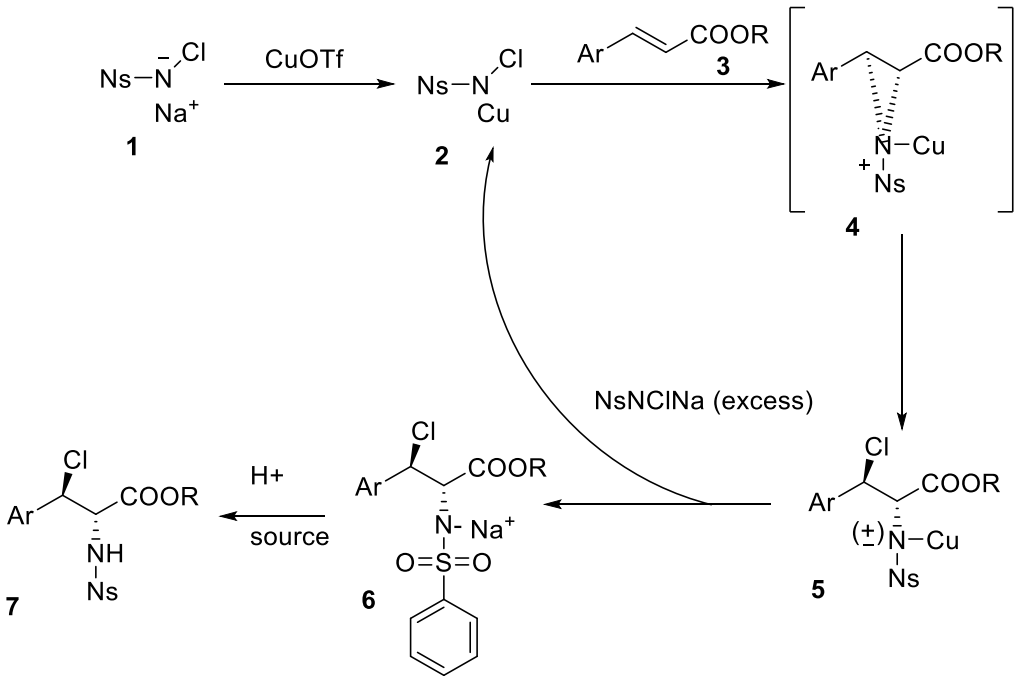


Figure 23. Co(OTf)/$Na_2S_2O_3$ promoted aminohalogenation reaction of olefins using N-halo-N-metallo-sulfonamide

2.2.3. Sulfonamides synthesis by C(sp)-H bond activation

Enesulfonamides are important intermediates are pronucleophiles for the metal catalyzed organic synthes.[64 65 66] Copper acetate in the presence of a 6,6'-dimethyl-1,10-phenanthroline based ligand system was used as the catalytic material for synthesizing(E)-β-chloro-ene sulfonamides under ambient conditions using DCM as a solvent with excellent regio- and stereoselectivity. The catalytic reaction cycle for the (E)-β-chloro-ene sulfonamides synthesis

using copper catalysts intiates with activation of **1** by **2** [copper(I)catalyst] to form intermediate **3**. The intermediate **3** reacts with alkyne **4** to form intermdiate **5**. The intermediate **5** undergoes intramolecular rearragement to form four membered cyclic intermediate **6**. In the next step, the intermediate **6** undergoes intermolecular rearragement to form three membered cyclic structure **7**. Finally, the three membered cyclic ring intermediate **7** undergors intramolecular rearragement to form final product **8** (Figure 24).[67]

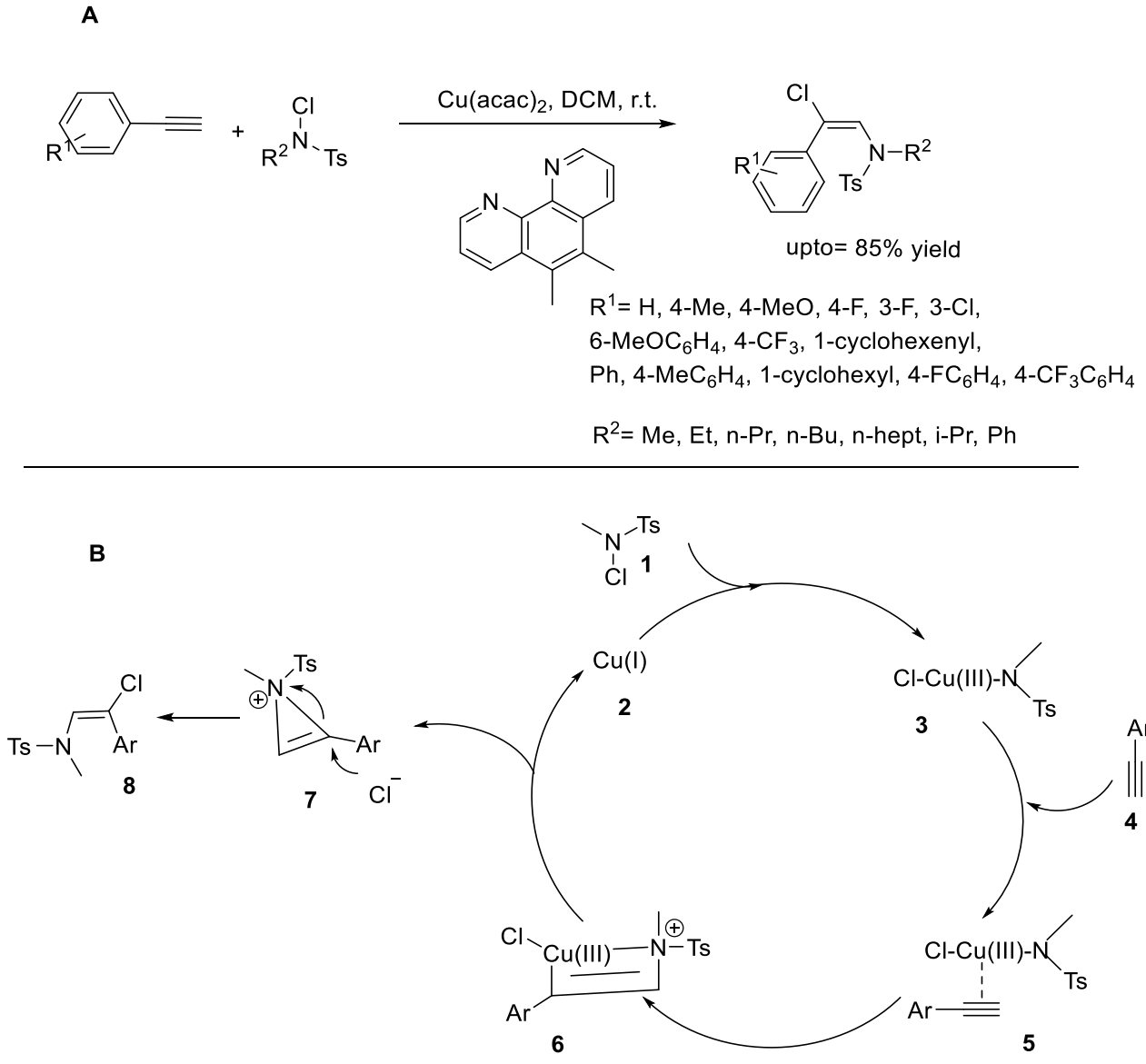
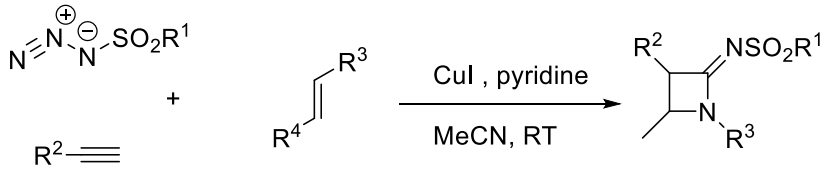


Figure 24. Copper acetate catalyzed synthesis of (E)-β-chloro-ene sulfonamides by reacting by chloroamination of alkynes

Azetidine derivatives are four membered nitrogen conaining heterocyclic compounds are important components of several natural products and structural building blocks for other important organic structures. [68] CuI/pyridine catalyzes synthesis of azetidine derivatives

attached with multiple substituents by three-component reactions involving cycloaddition of alkenes, alkynes and sulfonyl azides with excellent selectivity under ambient conditions. The desired multifunctional azetidine was formed with satisfactory yields (up to 90% yield) and stereoselectivity (>95:5)(Figure 25).[69]



R^1= Tol, 4-$(NO_2)C_6H_4$, 4-BrC_6H_4, 4-IC_6H_4, Me
R^2= Ph, 4-BrC_6H_4, 2-$(CF_3)C_6H_4$, 4-$(MeO)C_6H_4$, 3-Pyr, Bn, $PhCH_2$, $CH_2Cl(CH_2)_2$, $MeO_2C(CH_2)_3$,TMS
R^3 or R^4= Ph, 4-FC_6H_4, 4-$(MeO)C_6H_4$, Ph, Bn, 4-$(MeO_2C)C_6H_4$, 4-$(TMSCC)C_6H_4$, Ph, EtO_2C, SO_2Ph, Ph, 4-$(MeO)C_6H_4$

Figure 25. CuI/pyridine catalyzed cascade process involving synthesis of azetidine derivatives from alkenes, alkynes and *N*-sulfonylazetidin-2-imines

The mechanistic pathway for the transformation of N-sulfonylazetidin-2-imine initates by the cycloaddition of sulfonyl azide and copper acetylide to form intermediate **2**. The intermediate **2** librates nitrogen to form copper alkyamide **3**. Protonation of **3** furnishes the desired product sulfonylketenamine **4** and subsequent sepration of copper catalyst (See Figure 26).

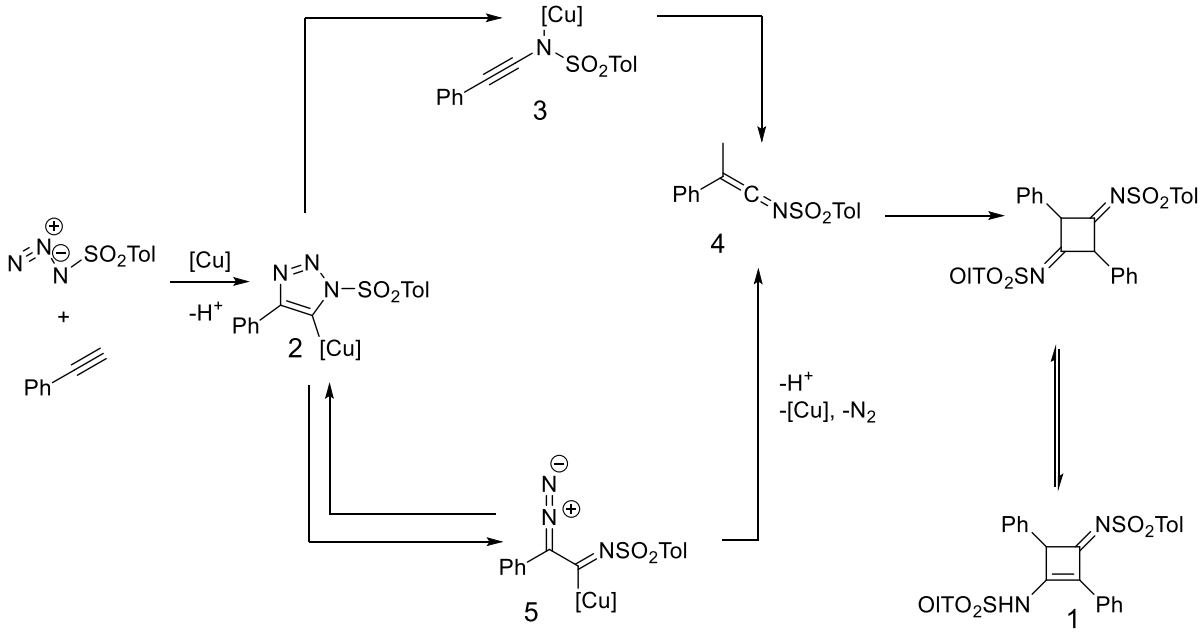


Figure 26. Mechanistic studies for the copper catalysed N-sulfonylazetidin-2-imine

$[Cu(CH_3CN)_4]PF_6$/tris(benzyltriazolylmethyl)amine(TBTA)/sodium ascorbate facilitated alkylation of terminal alkynes with sulfonyl azides resulting in formation of sulfonamides

with promising yields. The reaction was performed at room temperature using a t-BuOH/water system and proceeded via *in-situ* generation of copper (I) acetylides by single-step formal oxidative hydration of a triple bond. The mechanism for the sulfonamides synthesis from terminal alkynes and sulfonyl azides initiates with the copper mediated [3+2] cycloaddition **1** and **2** to form **3**. In the next step, release of nitrogen takes place to form intermediate **5**. Finally, **5** in the the acidic medium transforms to intermediate **7** followed by hydrolysis to form final product **8**. Alternatively, intermediate **3** transforms to **4** under acidic envirnoment. In the subsequent step, **4** underoges ring opening under equilibrium conditions to form intermediate **6**. Furthermore, intrermediate **6** converts to final products **8** via intermideate **7** (Figure 27).[70]

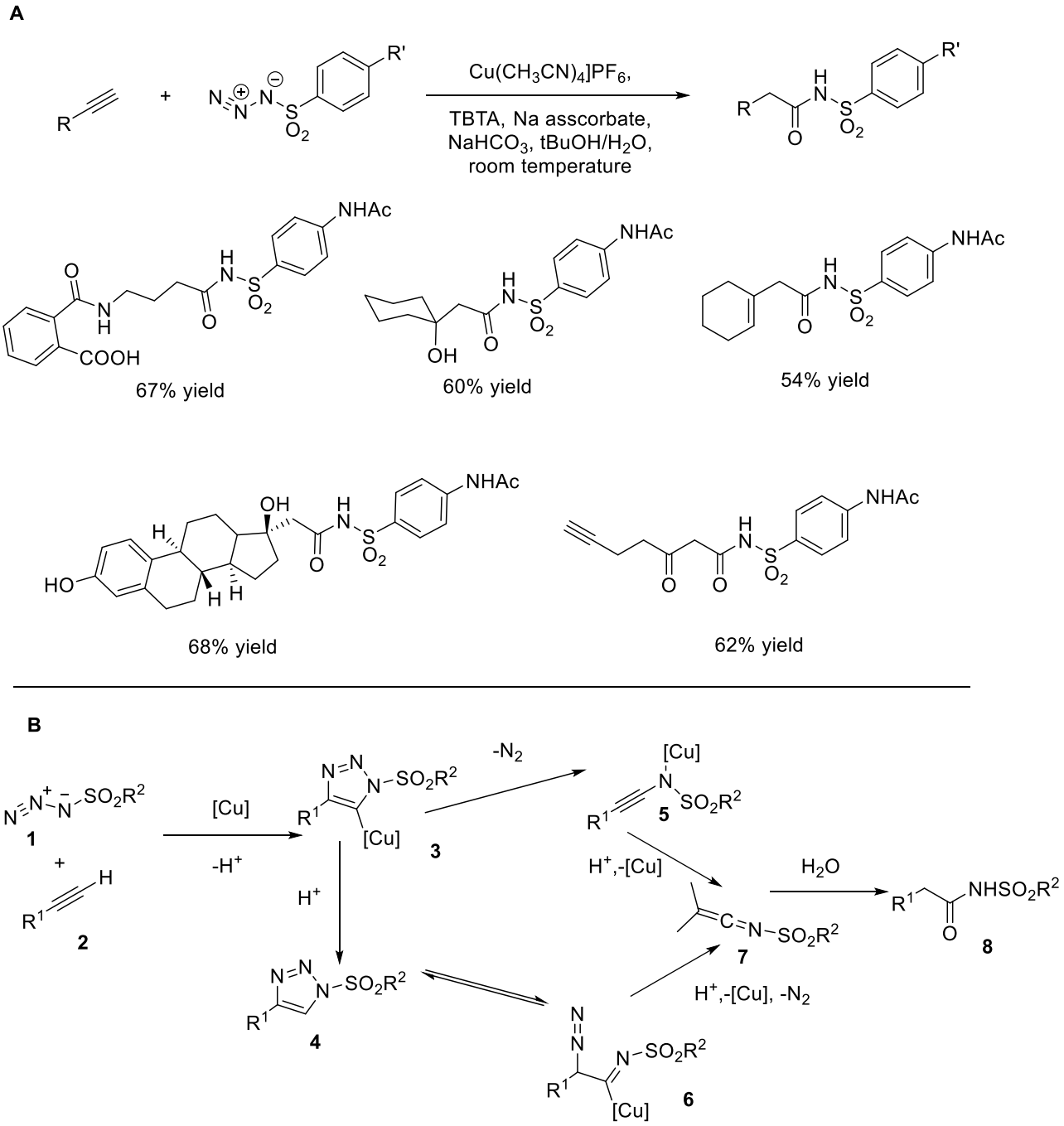


Figure 27. $[Cu(CH_3CN)_4]PF_6$/TBTA/sodium ascorbate promoted alkylation of terminal alkynes with sulfonyl azides to form sulfonamides

Copper(I) iodide/ K_2CO_3 at room temperature catalyzes 1,3-dipole cycloaddition/ketenimine formation/6π-electrocyclization/[1,3]-H shift cascade reaction to form 4-sulfonamidoquinolines. A variety of catalytic systems effectively synthesize a variety of 4-sulfonamidoquinolines with good yields (up to 84% yield), providing an excellent atom economy facile method under moderate reaction conditions. The mechanism for the Cu(I)

catalyzed synthesis of 4-sulfonamidoquinolines fromsulfonyl azides and alkynyl imines is presented in figure 28. [71]

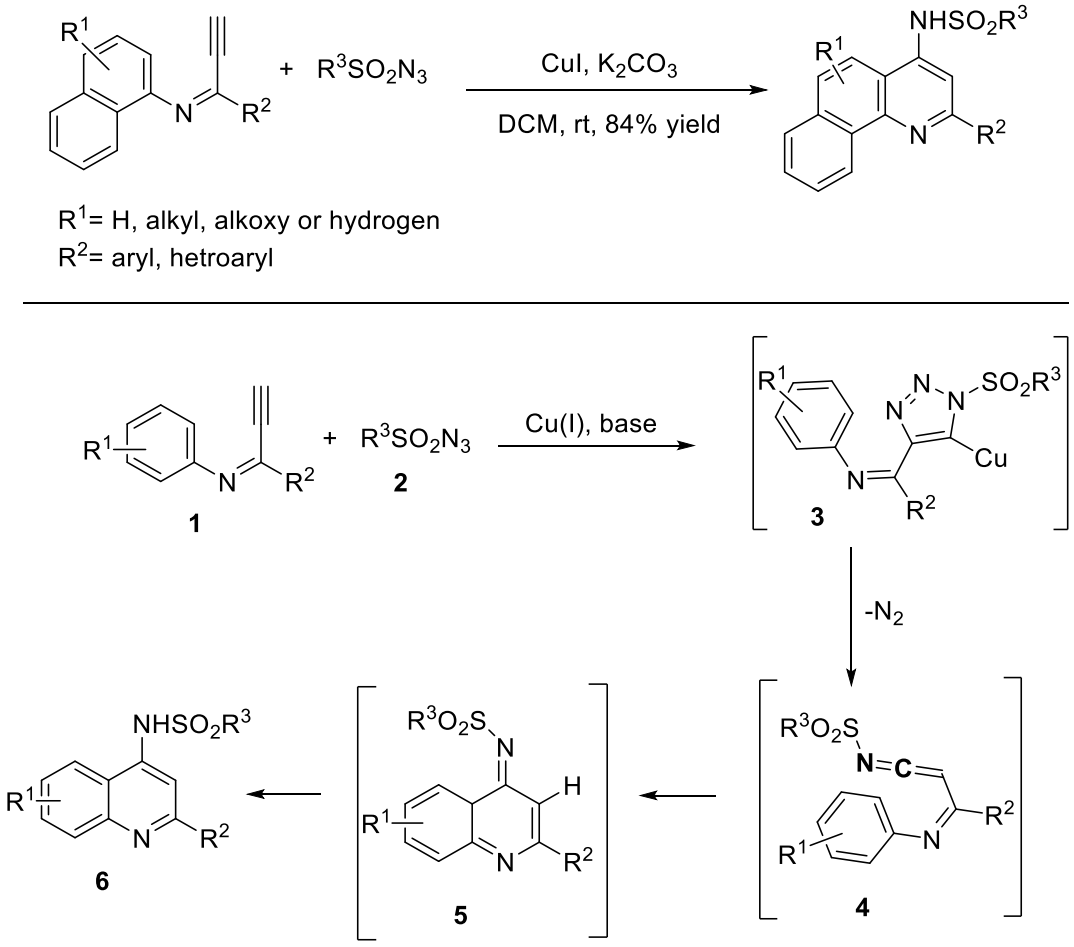


Figure 28. Copper(I) iodide/K_2CO_3 catalyzes the synthesis of 4-sulfonamidoquinolines fromsulfonyl azides and alkynyl imines

Copper(I)iodide/triethylamine (TEA) effectively catalyzed three-component reactions involving the synthesis of benzoxazoline-amidine derivatives from sulfonyl azides, terminal alkynes and Schiffs' bases. The reaction was performed at 0-5°C using tetrahydrofuran (THF) as a solvent. The proposed reaction mechanism involves azide-alkyne cycloaddition followed by intramolecular rearrangement using triethylamine as a base. The mechanistic pathway is clearly depicted in figure 29.[72]

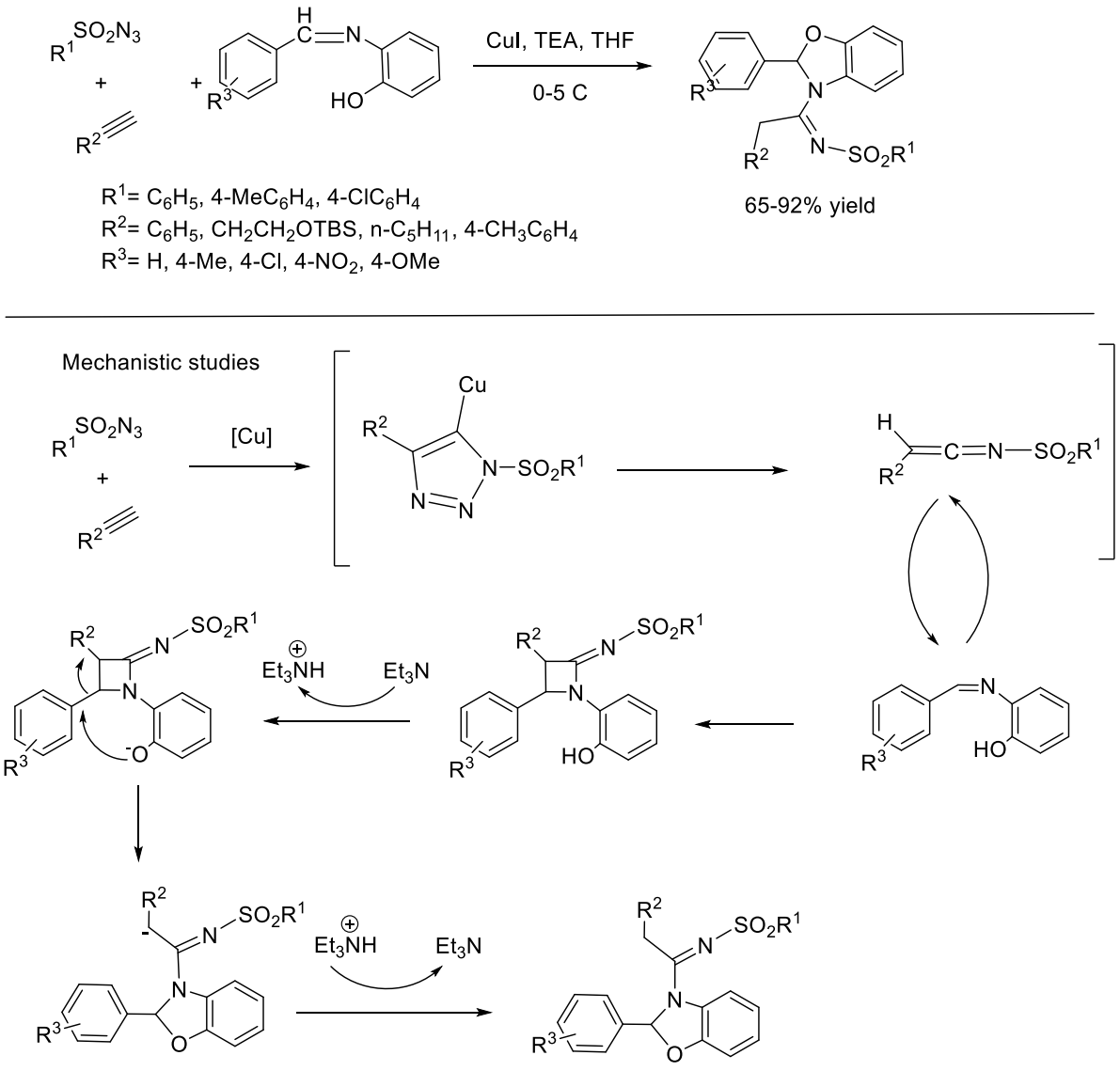


Figure 29. Copper(I)iodide/TEA catalyzed three-component reaction to form benzoxazoline-amidine derivatives

Copper(I) iodide effectively promoted three-component reactions to form N-sulfonylamidines using sulfonyl azides, terminal alkynes, and trialkylamines at 60 °C. The desired *N*-sulfonylamidines were synthesized with acceptable yields in an atom economic one-pot multicomponent domino process. Mechanism for the copper catalysed three component coupling of sulfonyl azides, terminal alkynes, and trialkylamines involves [3+2] cycloaddition, ring opening via elimination of nitrogen molecules and intramolecular rearrangement to form *N*-sulfonylamidines synthesis (Figure 30).[73]

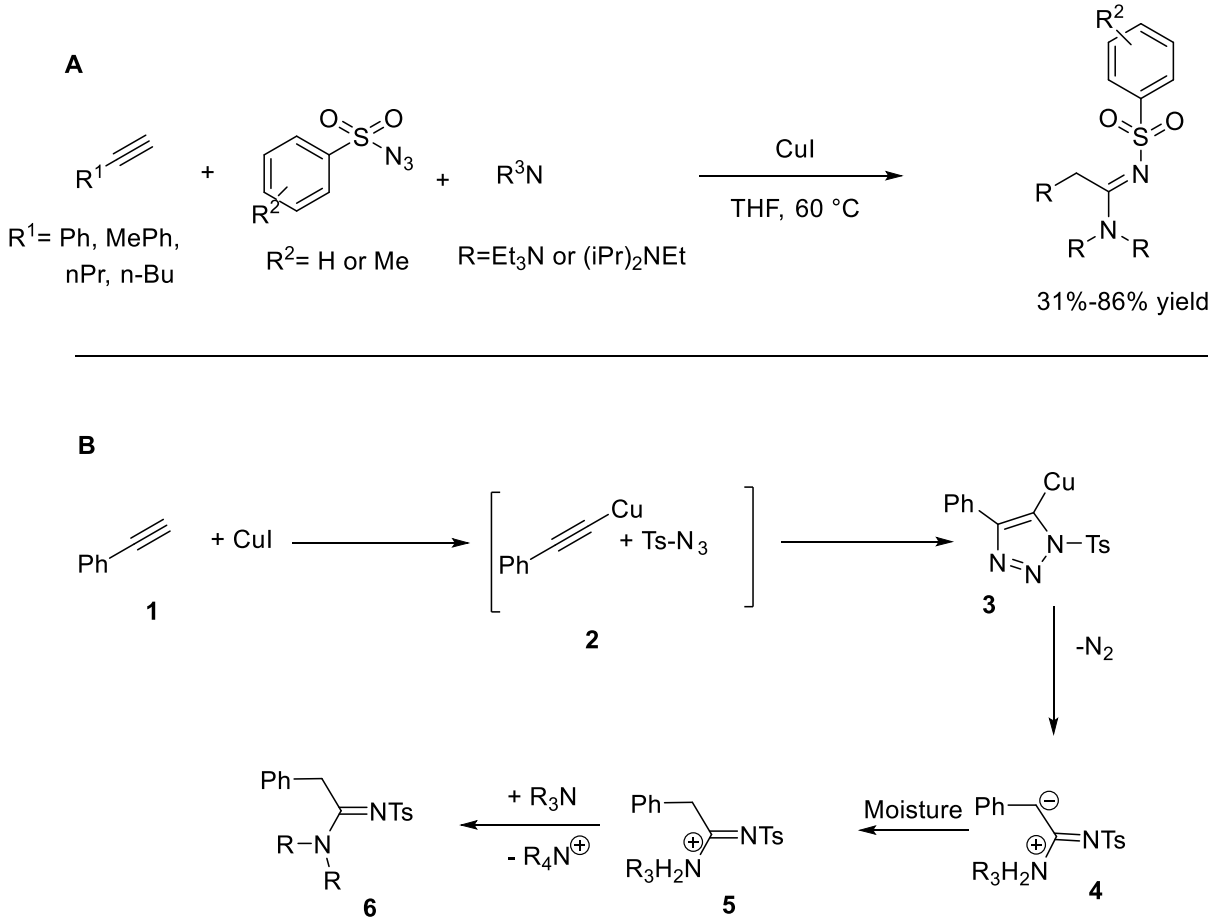


Figure 30. Copper(I) iodide effectively promoted *N*-sulfonylamidines synthesis of sulfonyl azides, terminal alkynes, and trialkylamines

$Cu(OAc)_2$ has proven to be an excellent catalytic material for assisting the cyclization of secondary anilines to form 1-*p*-tolylsulfonyl or 1-methylsulfonylindoles, having both electron-withdrawing and electron-donating groups present at the C2 position of indoles. The aforementioned methodology was effectively utilized to synthesize the cascade process involving sequential cyclization techniques involving the compounds with electrophilic parts present in the same molecule. The sequential cyclization process was initiated by treatment with KH providing the tricyclic ring systems limited to five- and six-membered rings. The cyclic mechanism for the synthesis of 1-*p*-tolylsulfonyl or 1-methylsulfonylindoles start with reaction Cu(II) catalyst with alkyne (**1**) to form intermediate (**2**). The intermediate **2** undergoes intermolecular rearrangement via intermediates **3**, **4** and **5** to form intermediate **6**. The intermediate **6** reacts with HCl to form final product **7**. Alternative mechanism for the aforementioned reaction involves intramolecular rearragement of **2** to form intermediates **5**

and **6**. The intermediate **6** rearrages in the presence of HCl to form final product **7**. (Figure 31).[74]

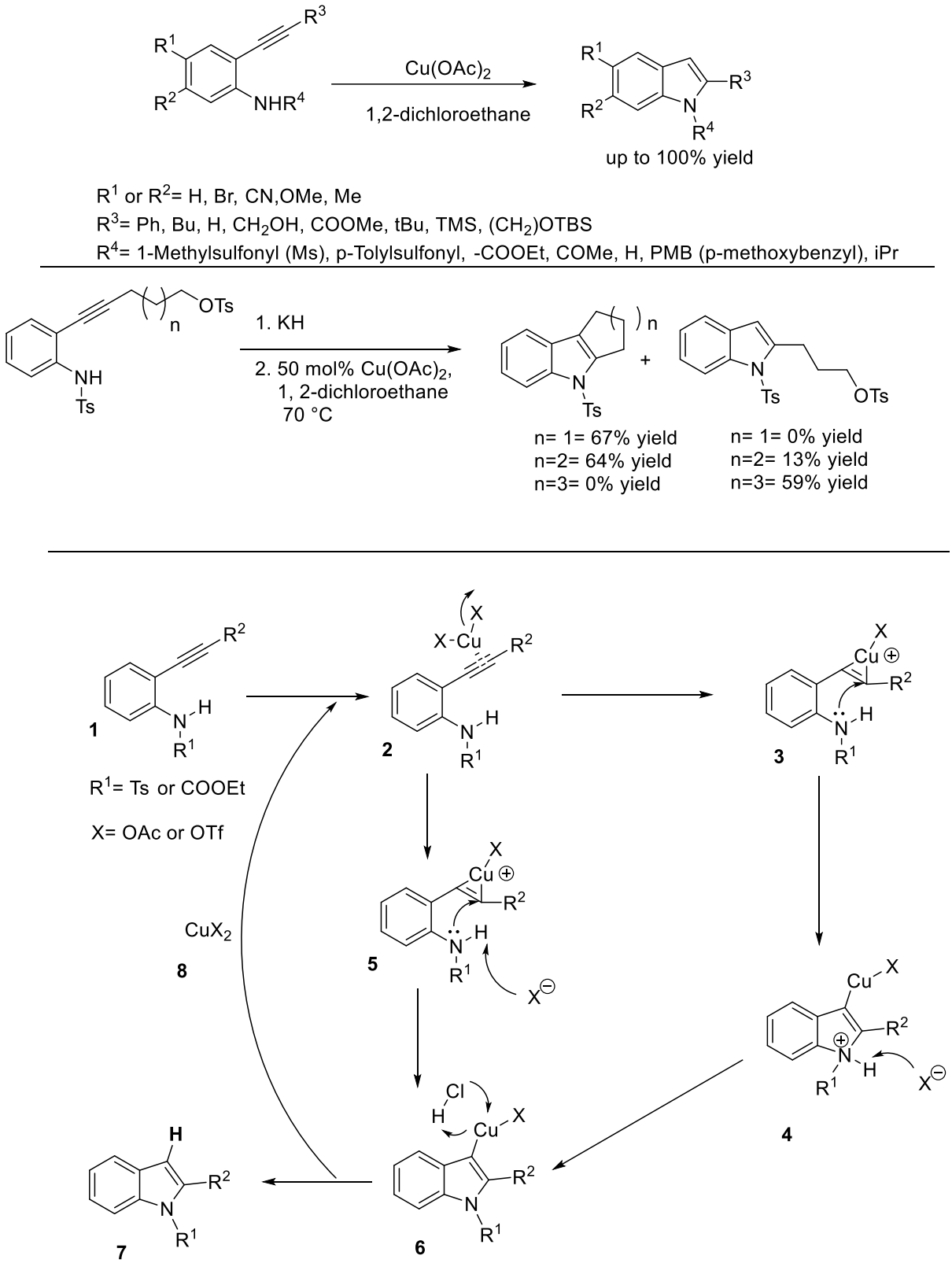


Figure 31. $Cu(OAc)_2$ catalyzed synthesis of indole ring 2-ethynylaniline derivatives

Yanamines, ynamides and yanasulfonamides are important class of heteroatom containing alkynes are signifance syntetic imtermediates for organic synthesis and bioactive compounds. These organic compounds possess internal triple bond that finds applications in the synthesis of variety of natural products. The high reactivity of the these yanmides is due to the presence of electron rich triple bond in close proximity of the strogly polarizing nitogen containing (amines, amides and sulfonamides) group. Copper(I)iodide/DIPEA effectively catalyzed the addition of ynamides to acyl chlorides orethyl chloroformate containing *N*-heterocycles compounds under ambient conditions. The copper-based facile and inexpensive carbon-carbon bond forming reaction provides a facile pathway for synthesizing abroad range of 3-aminoynones from aliphatic and aromatic acyl chlorides with competitive yields (up to 99% yield). 1,2-dihydro-*N*-heterocycles were synthesized by adding pyridines and quinolines in similar reaction conditions, providing good to high regioselectivity with more than 95% yield. The copper catalyzed cyclic reaction mechanism for the synthesis of these heterocyclic compounds starts with reaction of **1** (CuI) and **2** (yanamide) to form intermediate **3**. The intermediate **3** in the presence of based rearranges to form intermediate **4** and **5**. Finally, intermdiates **5** rearrages to form diversity of heterocyclic compounds (Figure 32).[75]

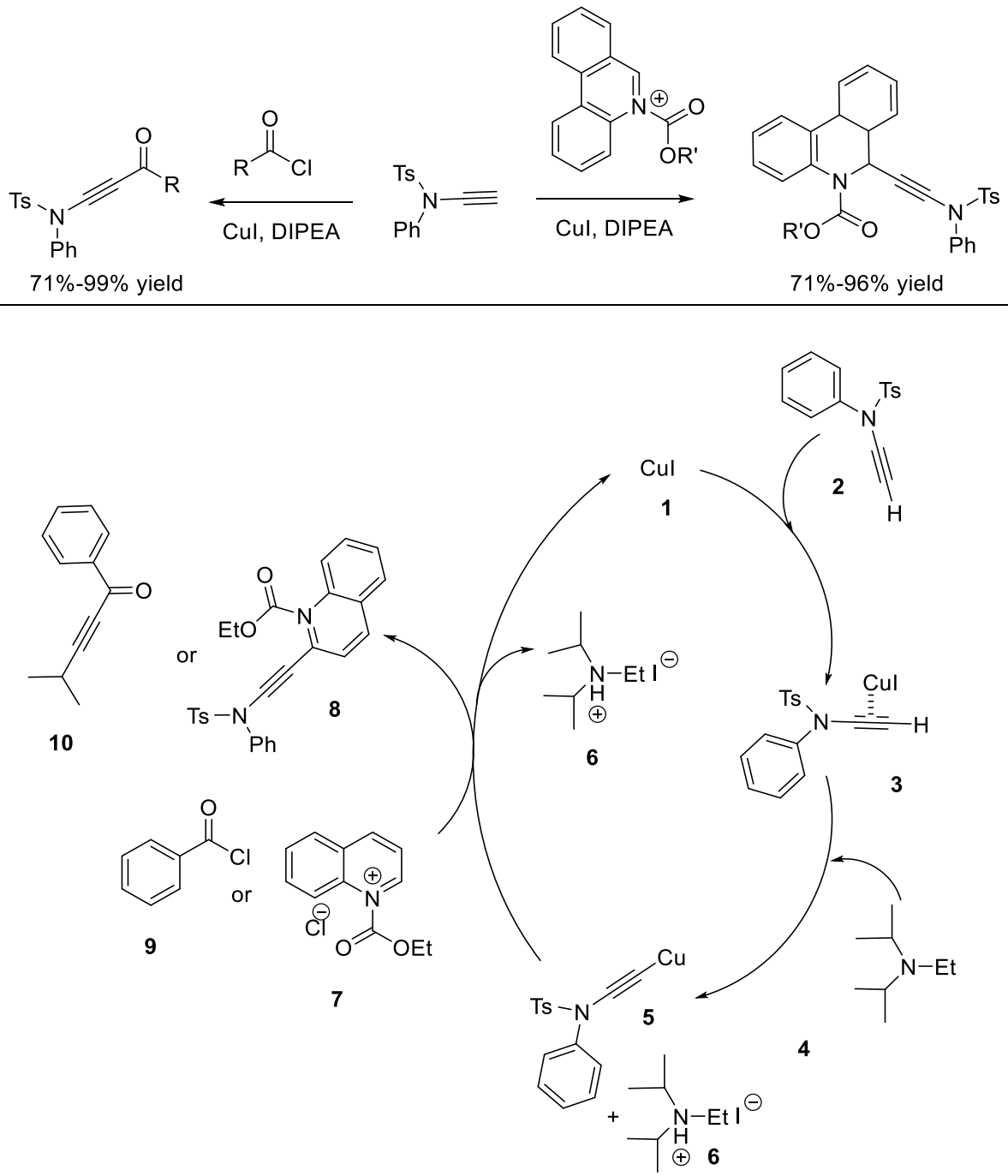


Figure 32. Copper(I)chloride catalyzed transformation of ynamides to acyl chlorides and activated *N*-heterocycles

α-Keto amides are important pharmacophores finding applications in biological and medicinal applications. These α-Keto amides possess multiple reactive centres via the electrophilic and nucleophilic characters are synthesised via the reforming of diverse array of C–C, C–O, C–N and C–H bonds. α-Ketoamides are important component of different medicinal compounds like human coronavirus (HCoV), SARS-CoV-2.[76] [77] [78]

Copper(I)chloride effectively promoted photochemical (visible-light mediated) oxidation of C≡C bond present in ynamides/ynamines under aerobic conditions under ambient conditions. The catalytic system tolerated various functional groups yielding α-ketoimide/α-ketoamide skeletons in excellent yields (78–92%). Mechanistic studies reveal that there was an *in-situ* copper(I)-coordinated π-complex (λ_{max}=460 nm) held responsible for the visible light-promoted synthesis of α-Ketoimides/α-Ketoamides. Mechanism for the aerobic copper catalysed photochemical oxidation of ynamides/ynamines under aerobic and ambient conditions to form α-ketoimide/α-ketoamide is presented in figure 33.[79]

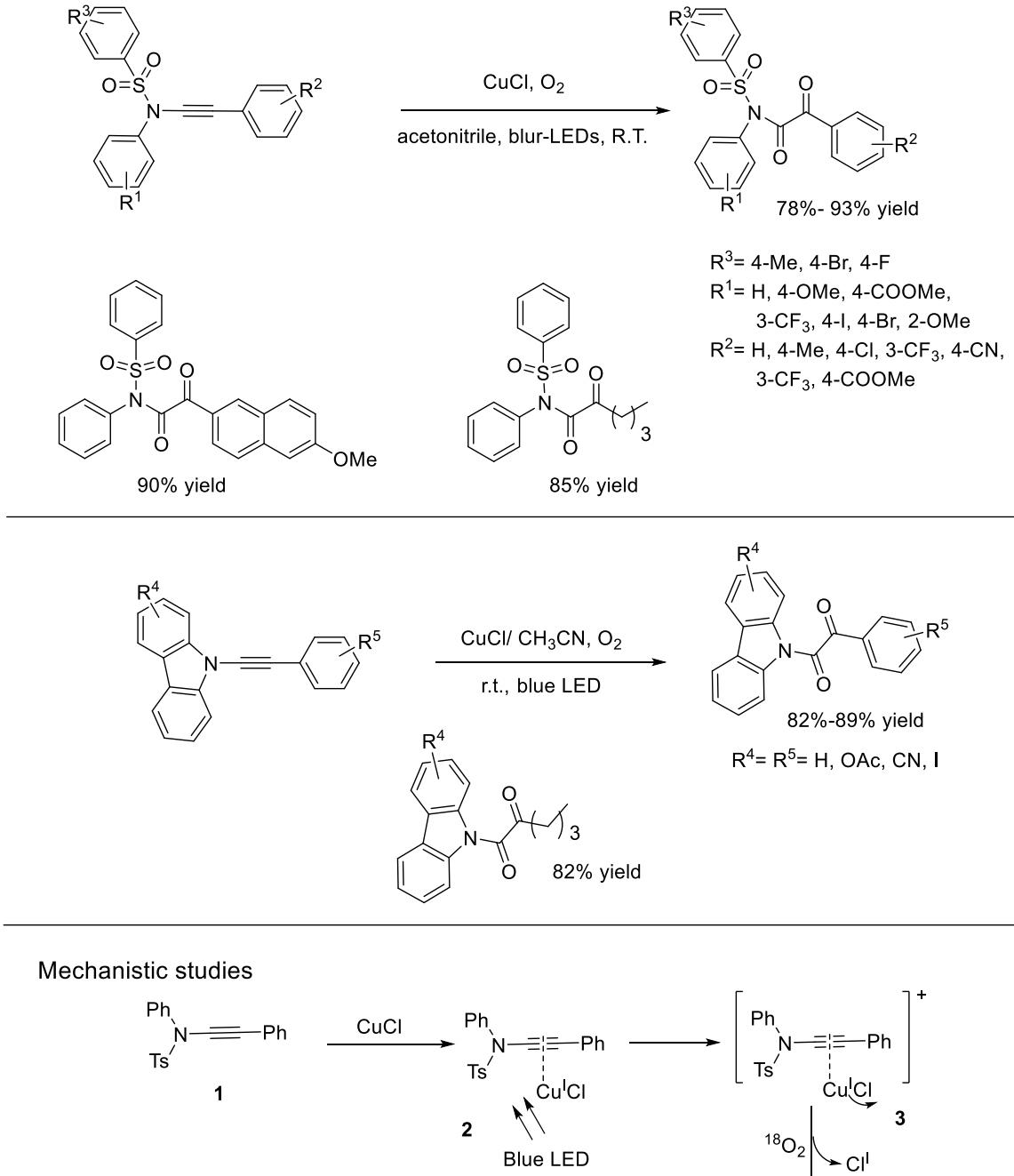


Figure 33. Copper(I)chloride promoted photochemical oxidation of ynamides/ynamines under aerobic and ambient conditions

Copper(I)iodide/tri-ethylamine promoted the synthesis of *N*-sulfonyl amides by reacting terminal alkynes, sulfonyl azides and water under moderate reaction conditions. The catalytic

system provided an efficient methodology for the synthesis of the diversity of alkynes and sulfonyl azides in the presence of water to yield the desired amides in good to excellent yields. The catalytic system efficiently resisted the transformation of various labile functional groups (Figure 34).[80]

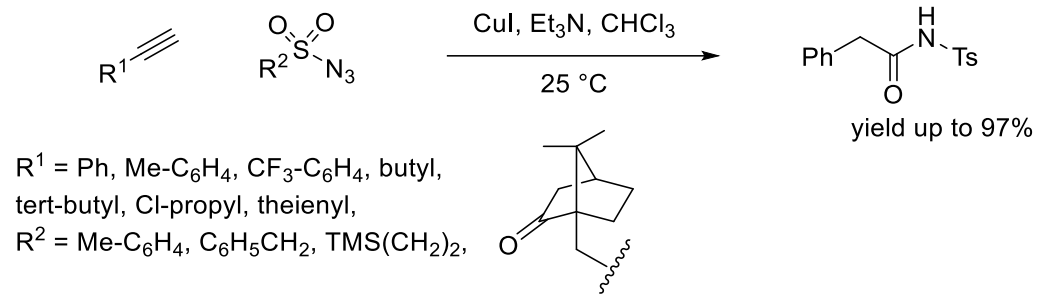


Figure 34. Copper(I)iodide/tri-ethylamine catalyzed synthesis of sulfonamides three-component reaction

Copper (I)iodide/tri-ethyl amine catalyzes coupling of alkynes with sulfonamides in an aqueous medium under ambient and environmentally benign conditions affording the synthesis of desired amidines or imidates. The catalytic system was also used to produce β-hydroxy N-sulfonamides in good yields by reacting propargyl alcohols with p-toluenesulfonyl azide.The catalytic system reactseffectively with propargyl alcohols and sulfonyl azides to form β-hydroxy *N*-sulfonamides in good to excellent yields. Furthermore, the above-mentioned technique was effectively used for the stereoselective synthesis of polyhydroxy amides via the aldol-surrogate strategy (Figure 35).[81]

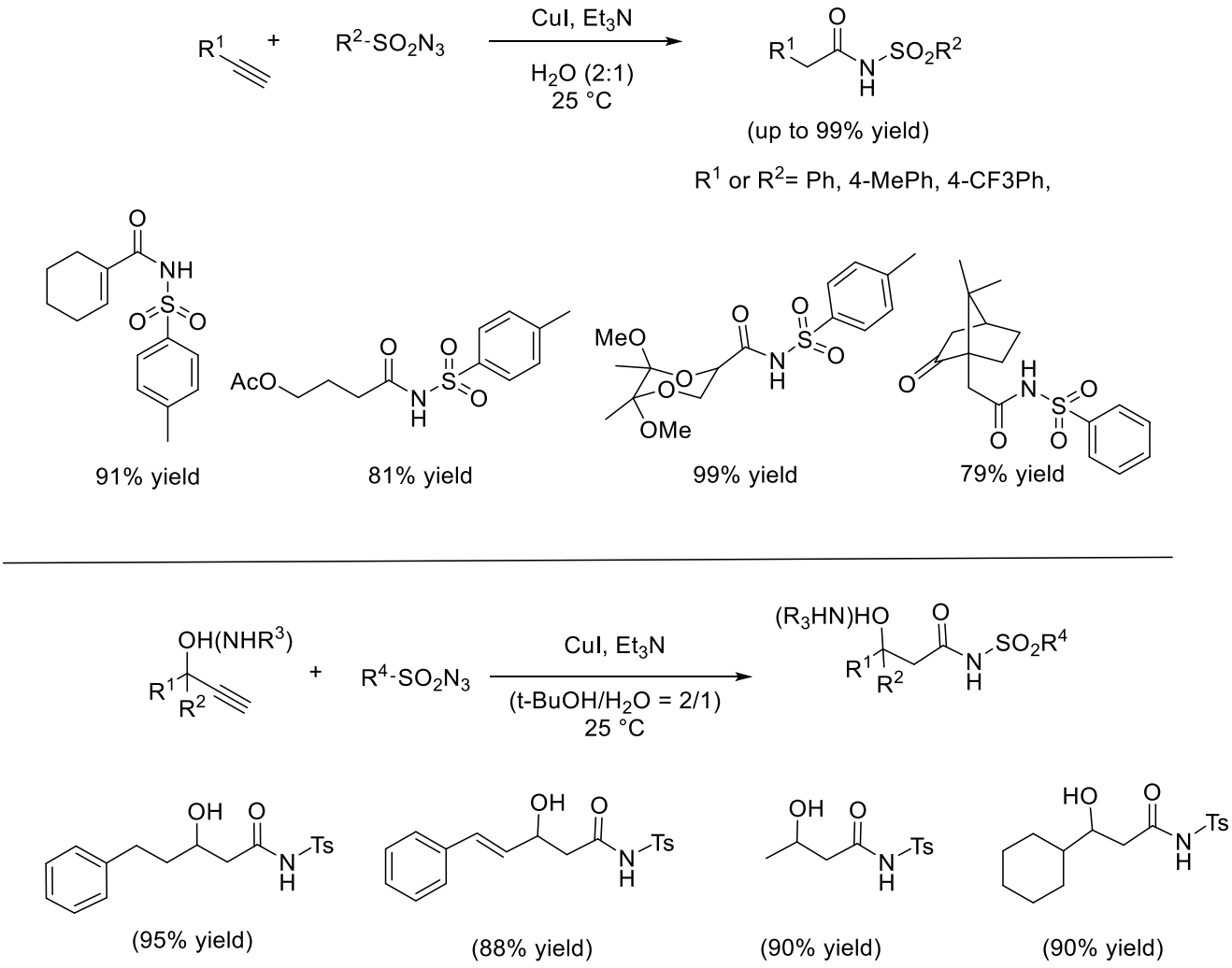


Figure 35. Copper (I)iodide/tri-ethyl amine catalyzes multicomponent method for the synthesis of amidines or imidates

$CuSO_4 \cdot 5H_2O$/1,10-phenanthroline K_3PO_4 was used for the environmentally benign protocol for the synthesis of ynamides, including sulfonyl and heteroaromatic amine from amides and alkynyl bromides. In the presence of toluene as solvent the corresponding ynamides in good to excellent yields (Figure 36) **[82].**

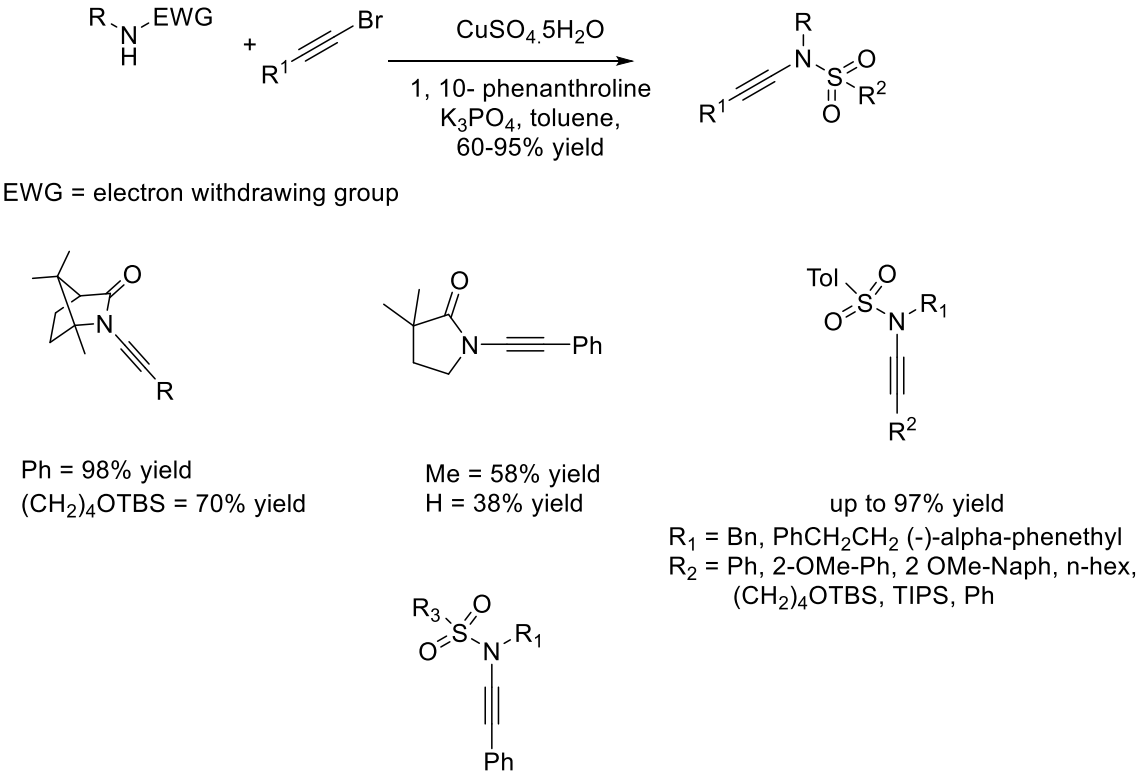


Figure 36. $CuSO_4 \cdot 5H_2O$/1,10-phenanthroline catalyzed synthesis ynamides alkynyl bromides with heteroaromatic amine

2.3. Sulfonamide synthesis by amidation of -OH and -SH bond functionalization

Copper(I) iodide-bipyridine was used as the catalytic material for synthesizing sulfinamides from thiols or thioethers and amines under facile and aerobic reaction conditions with NH_4PF_6 as nitrogen source to sulfinamides in excellent yields. The catalytic cycle (**A**) for the Cu(I) catalysed sulfinamides from thiols or thioethers and amines initates with the activation of N-H bond of amines (**2**) by Cu(I) (**1**) catalyst to form intermediate **3**. The intermediate **3** reacts with molecular oxygen and H^+ (**4**) to form intermediate **5**. In the next step, intermediate **5** reacts with thiol to form intermediate **6**. The intermediate **6** rearranges to form intermediate **10** followed by the regeneration of the catalyst. Alternative pathway (**B**) for the copper catalysed sulfinamides involves the reaction of **3** with $(ArS)_2$ (**6**) to form the intermediate **7**. In the next step, the intermediate **7** rearrages to form **10** along with the release of Cu(I) intermediate (**8**). The intermediate **8** oxidzes under aerobic condition to form

intermdiate **9**, followed by reaction with amine to form intermediate **6**. The intermediate **6** is converted to intermediate **10** under aerbic and acidic condition and simultaneous regenration of the catalyst. Finally, copper under aerobic conditions assist in the oxidation **10** to form final product **12** (Figure 37).[83]

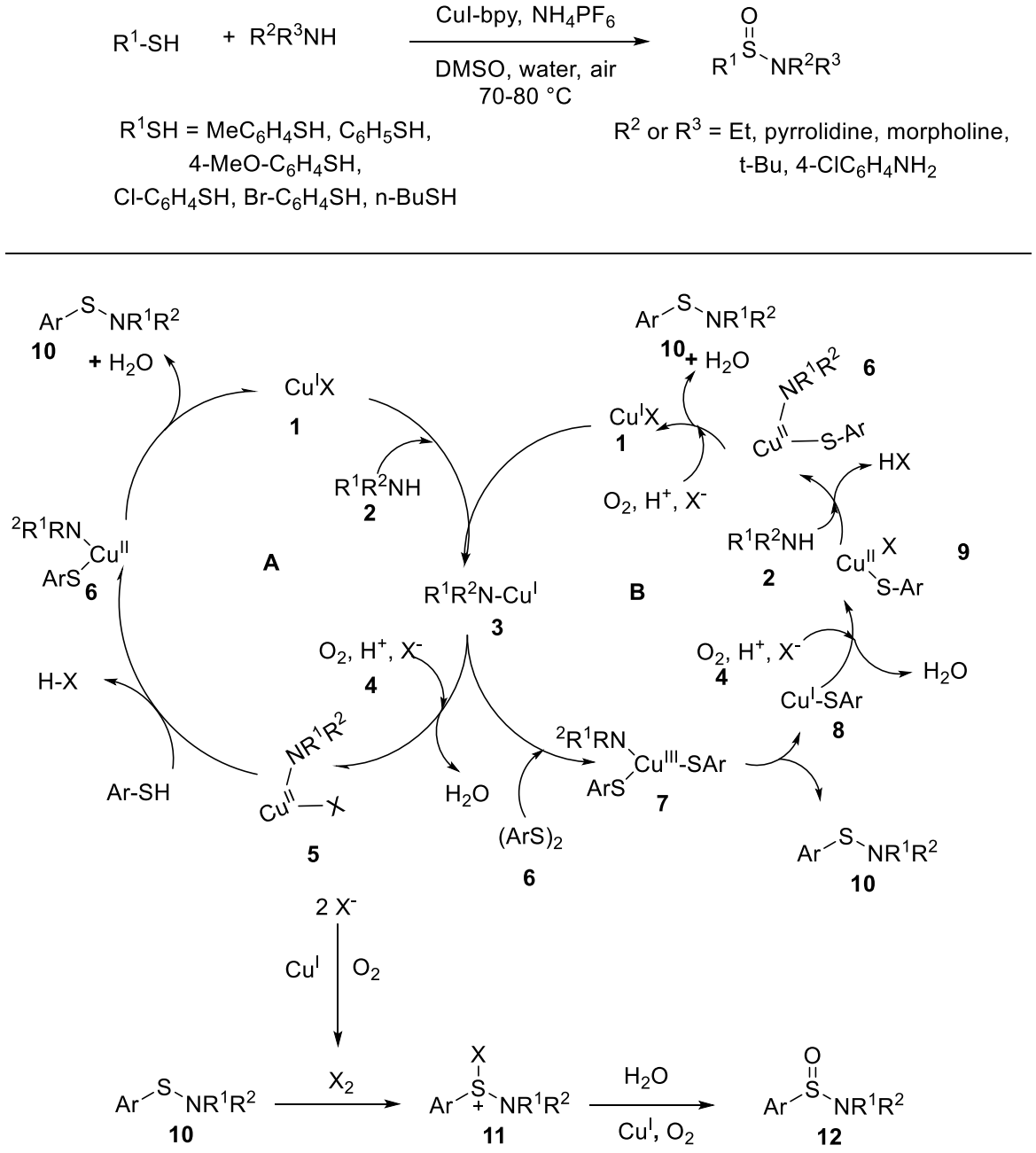


Figure 37. Copper(I) iodide-bipyridine catalyzed synthesis of sulfinamides from thiols or disulfides with amines

Copper acetate [$Cu(OAc)_2$]/K_2CO_3 catalyzes *N*-alkylation of sulfonamides with alcohol to form N-alkylated-sulfonamides and alcohols with promising yields. The catalytic reaction proceeded in the aerobic environment at 150°C. The mechanistic studies performed using

benzyl alcohol and benzyl alcohol-d_7 with *p*-toluenesulfonamide show that kinetic isotope effect (*k*H/*k*D) for dehydrogenation and hydrogenation benzyl alcohol were 3.287 (0.192) and 0.611 (0.033) respectively to form *N*-benzylidene-*p*-toluenesulfonamide intermediate suggesting that alcohol dehydrogenationoccurred at the rate-determining step (Figure 38)**[84].**

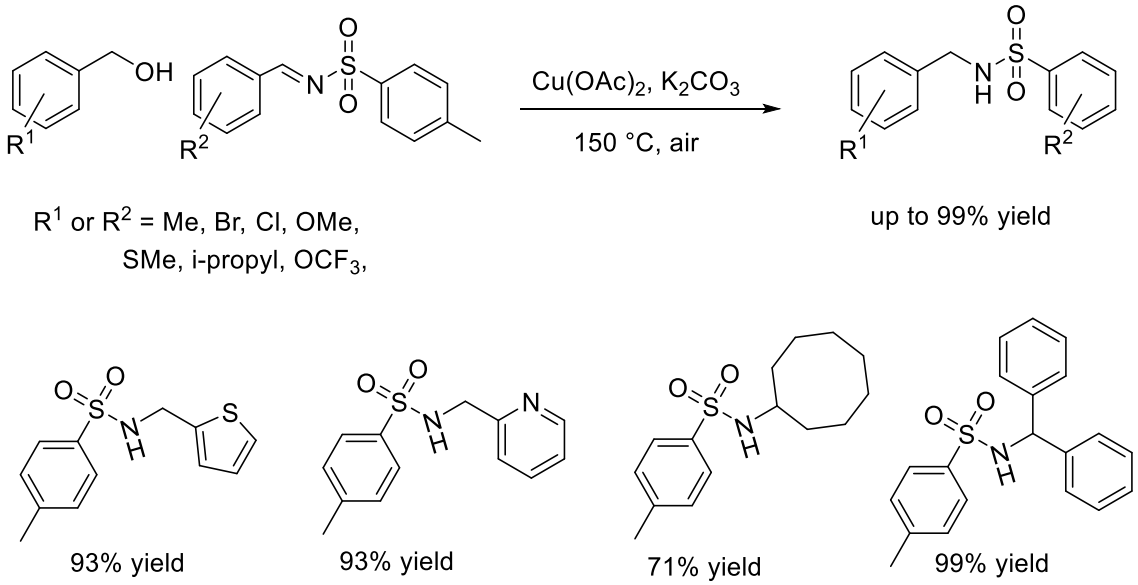


Figure 38. $Cu(OAc)_2/K_2CO_3$ catalyzes *N*-alkylation of sulfonamides with benzylic alcohols

$Cu(OAc)_2/K_2CO_3$ promotes one-pot atom economic reaction between alcohols and sulfonamides to generate water as the sole byproduct. The transhydrogenative C-N bond forming reaction resulted in a broad range of bis-sulfonylated amidines with satisfactory yields. (Figure 39) **[85]**

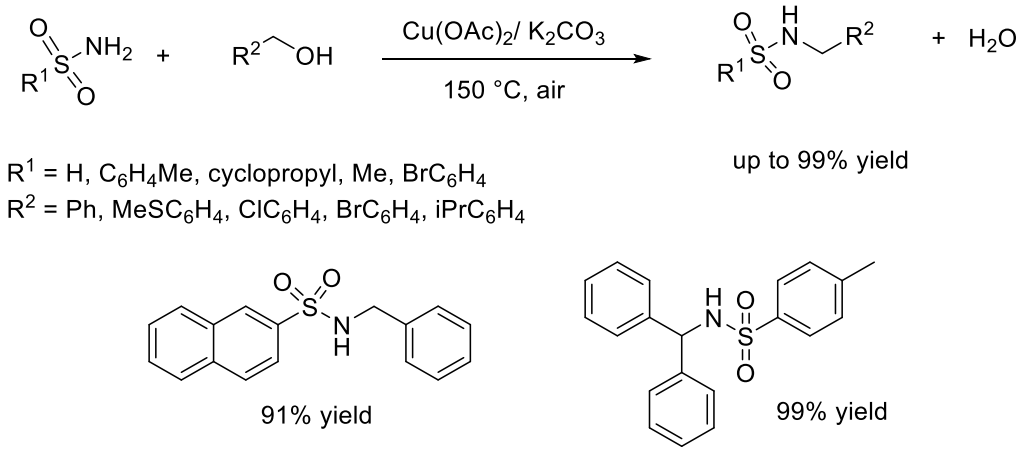
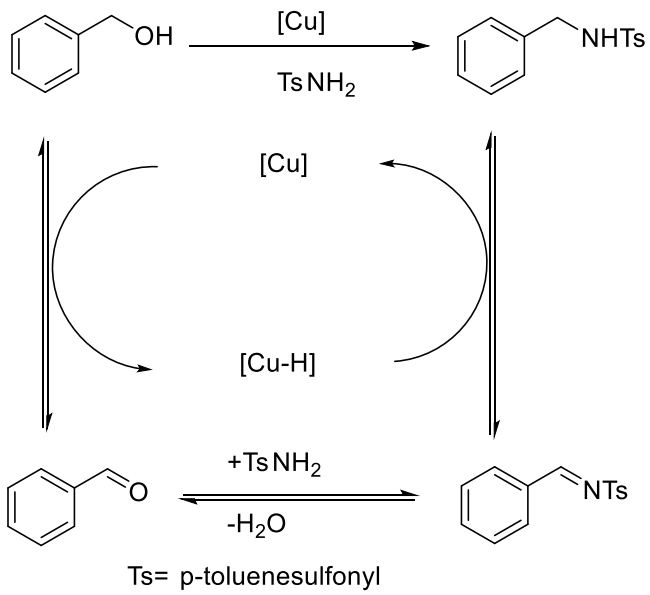


Figure 39. $Cu(OAc)_2/K_2CO_3$ catalyzes alkyation of sulfonamides with alcohols

Mechanism for the the copper catalysed alkyation of alkylation of sulfonamides with alcohols involves copper mediatated aerobic oxidation of alcohol to the aldehyde followed by follwed

by reaction with amine to form imine intermedate. The imine intermediate is reduced to yield the final product according the stretagy demonstrated in the figure below (See Figure 39).



Proposed mechanism for alkylation of sulfonamides with alcohols

Figure 39. Mechanism for the alkylation of sulfonanmides with alcohols

Copper acetate $Cu(OAc)_2.H_2O/K_2CO_3$ was used as the catalyst under ligand-free conditions for the N-alkylated sulfonamides via coupling of alcohols with sulfonamides at 135 °C. The reaction proceeded by aerobic oxidation of alcohols to aldehydes alcohol activation strategy. The desired N-alkylated amides were synthesized in good to excellent yields. Mechanism for the copper catalyzed N-alkylated sulfonamides synthesis initiates with the oxidation of alcohol **1** to the aldehyde **2** followed by base condensation of amine **3** to form imine intermediate **4**. In the final step, **4** undergoes reduction to form N-alkylated sulfonamides **5** (Figure 40).[86]

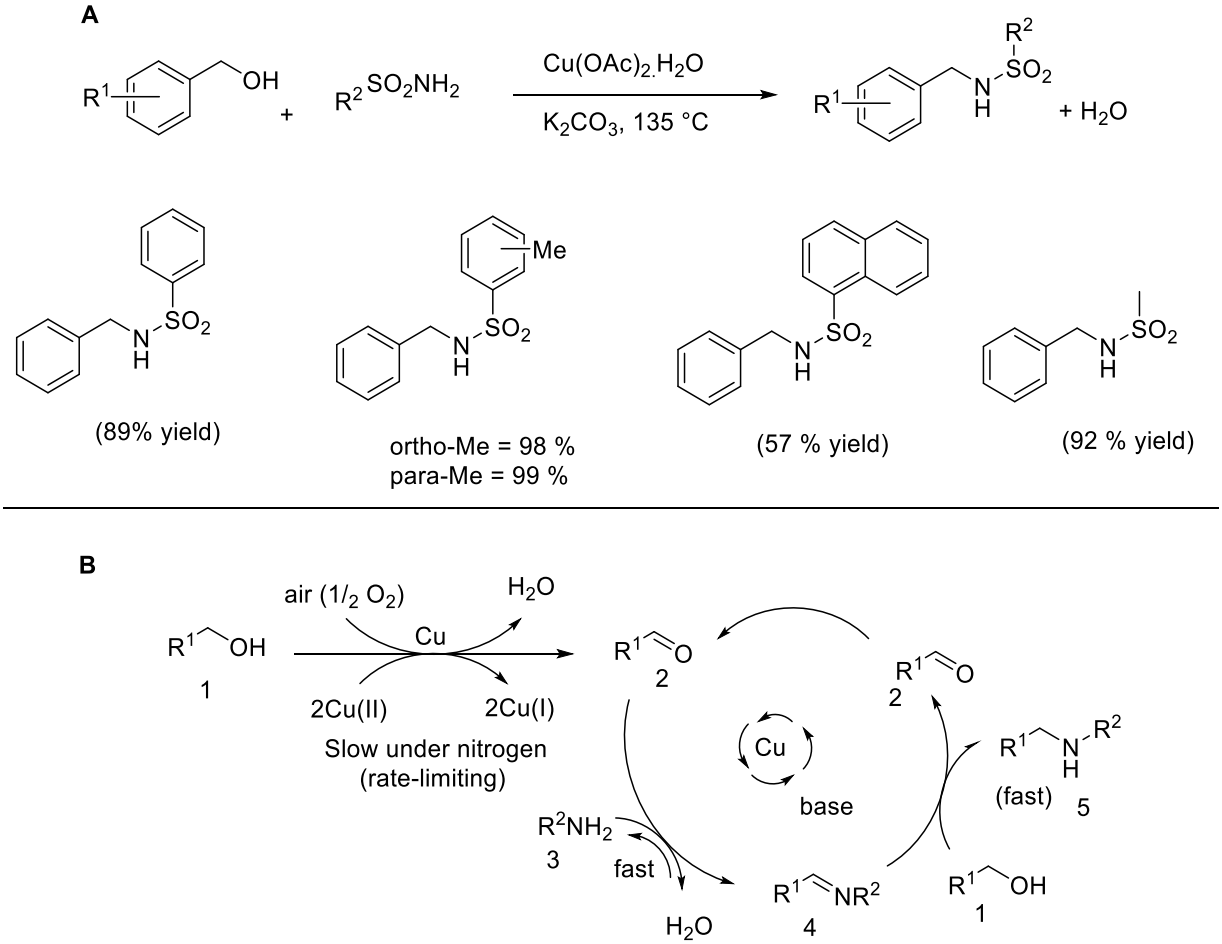


Figure 40. $Cu(OAc)_2.H_2O/K_2CO_3$ catalyzed aerobic *N*-alkylation of amides and amines with alcohols

CuCl,$Cu(OAc)_2$/cinnamic acid effectively catalyzed S–N bond-forming reaction by a facile method to synthesize thiols and DMF under ambient conditions and aerobic environment. The reaction proceeded by a radical mechanism with moderate to good yields. The catalytic cyclic mechanim for the copper catalzed synthesis of N-alkylated sulfonamide. Mechanism for the copper catalyzed synthesis of sulfonamides form thiol and DMF intiates with the oxidation of **14** to form intermediate **1** by copper salt. In the subsequent steps, intermediate **1** is transformed to **4** by carboxylate anion **2,** followed by oxidation of **4** to form radical intermediate **5** that exists in equilibrium with intermediate **6.** In the parallel reaction, DMF reacts with carboxylic acid **8** to form amine intermediate **9**. In the following step, **9** reacts with LnCu(II) (**11**) to form intermediate **12**. The resulting intermedate **12** reacts with **6** to form final product **13** (Figure 41).[87]

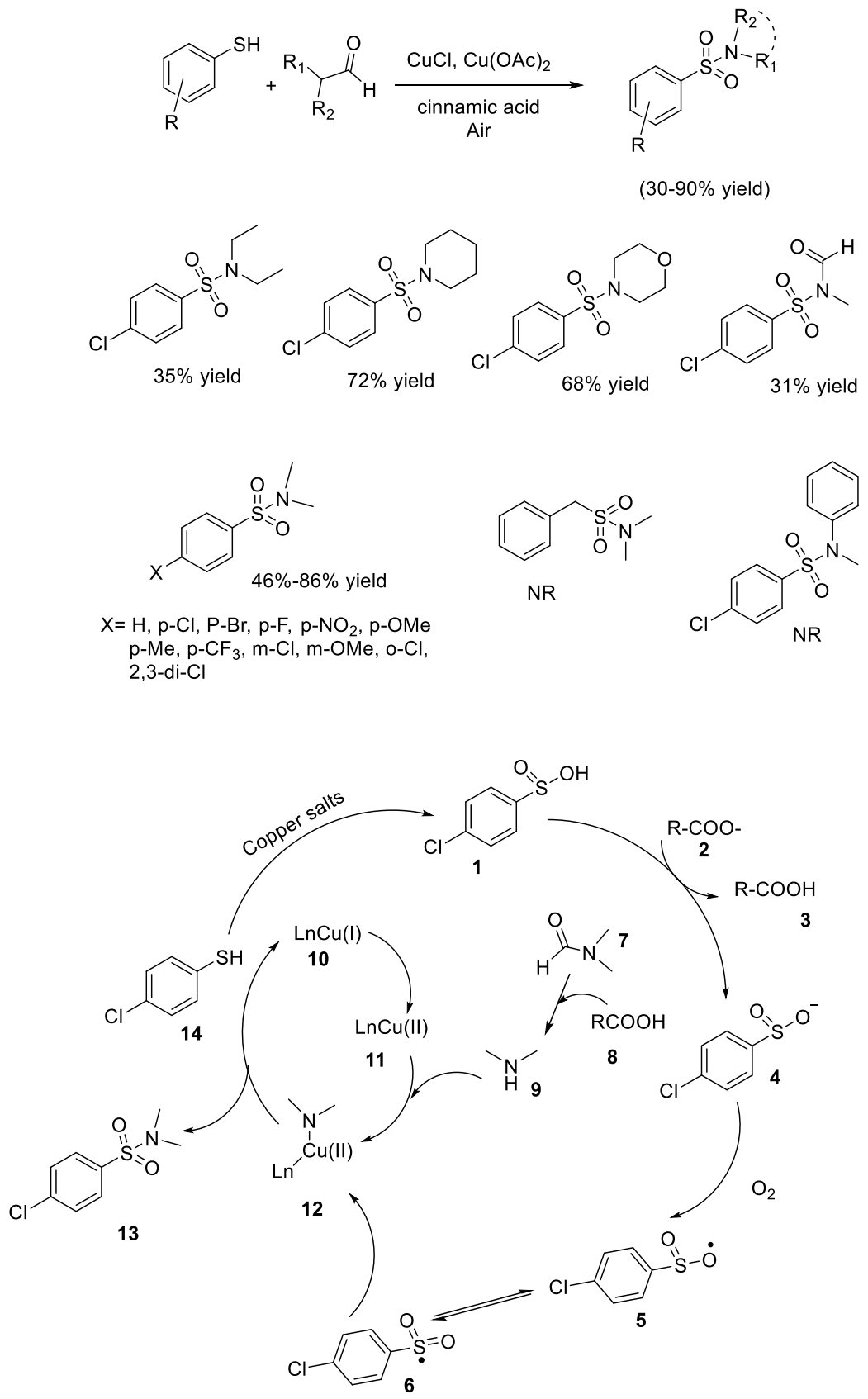


Figure 41. CuCl,$Cu(OAc)_2$/ cinnamic acid catalyzed synthesis of sulfonamide from thiols and DMF under aerobic conditions

2.4. Sulfonamide synthesis by N-H bond activation

Copper bromide ($CuBr_2$) effectively promoted sulfonamides synthesis by reactingsodium sulfinates and amines with 1 atm O_2 or DMSO as the oxidant. Mechanistic investigations reveal that the transformation proceeded by a single electron transfer (SET) pathway, resulting in a broad range of sulfonamides (Figure 42). [88]

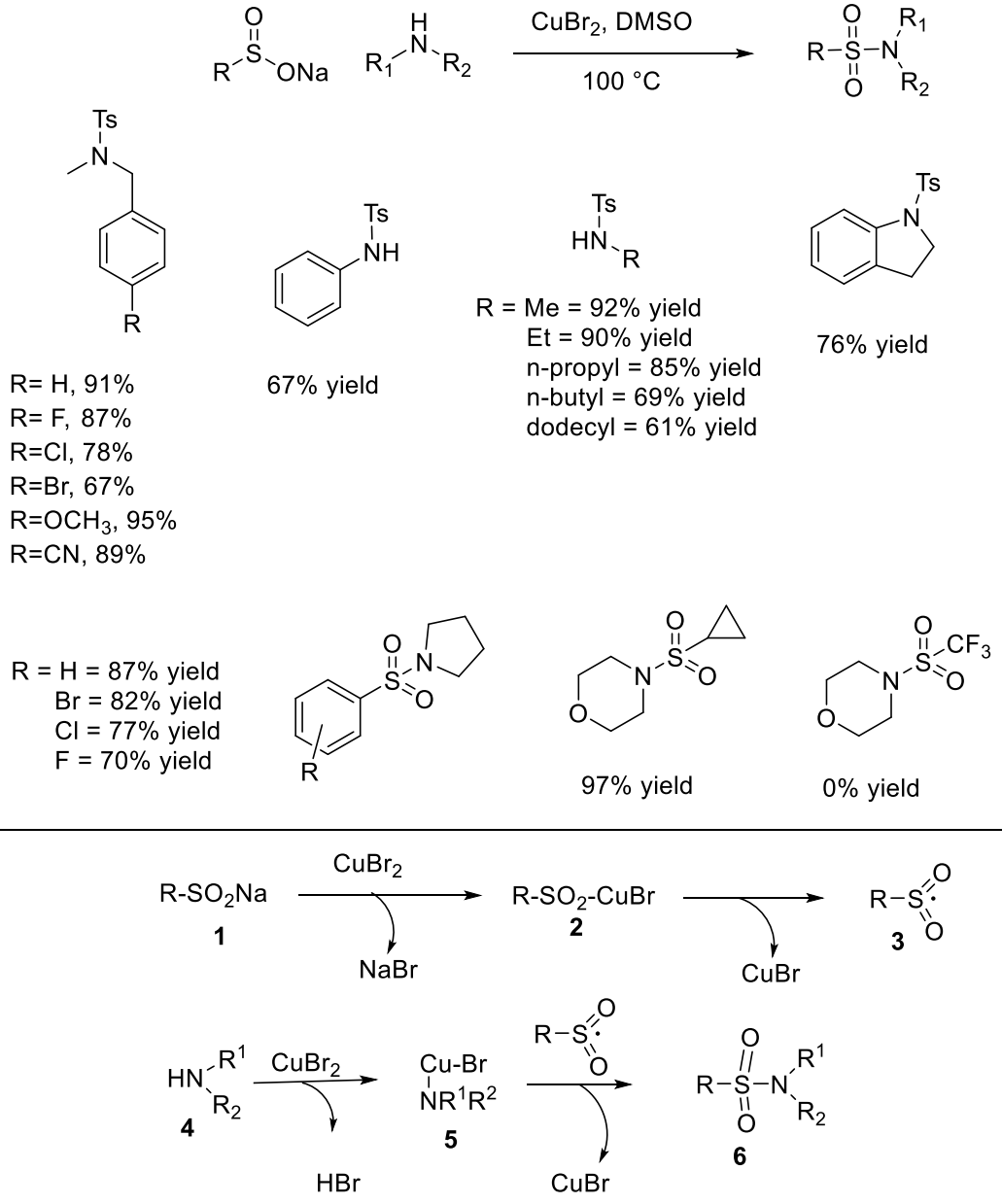
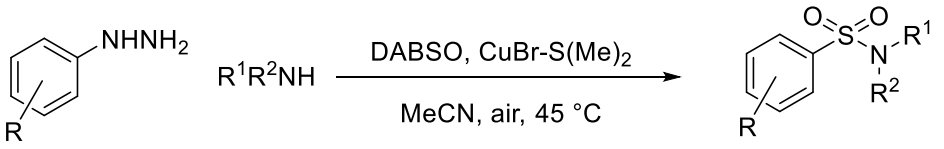
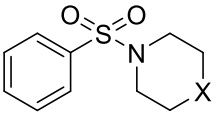


Figure 42. Copper bromide ($CuBr_2$) promoted sulfonamides synthesis from sodium sulfinates and amines

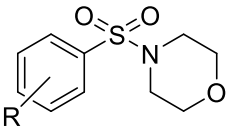
CuBr-$S(Me)_2$ effectively promoted aerobic cross-coupling of hydrazines witha wide range of primary, secondary amines as nitrogen sources and 1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) (DABSO). The catalytic reaction proceeded using acetonitrile as a solvent at 45 °C without using any additives. The catalytic system tolerated a variety of substituted hydrazines as well as amines affording a variety of sulfonamides with promising yields. Mechanism for the copper catalyzed sulfonamide synthesis starts with oxidation of hydrazine **1** to form radical intermediate **3** (via the intermediate **2**). The radical intermediate **3** releases nitrogen molecule to form radical intermediate **4** followed by addition of SO_2 to form **5**. In the following step, the intermediate **5** reacts with **5a** to form intermediate 6 followed by reaction with amine **7** to form intermedate **8**. Finally, intermediate **8** converts to **9** and subsequent regereration of catayst. (Figure 43).[89]



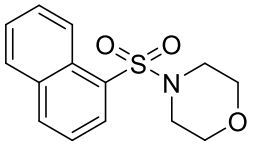
1,4-diazabicyclo[2.2.2]octanebis(sulfur di-oxide)(DABSO)



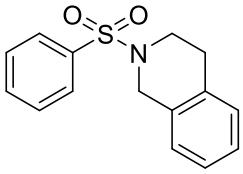
X = O = 69% yield
CH_2 = 64% yield
S = 37% yield
NMe = 43% yield
NPh = 54% yield



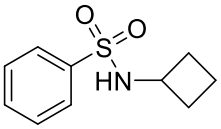
R = Me = 72% yield
t-Butyl = 63% yield
OMe = 65% yield
Cl = 57% yield
CF_3 = 55% yield



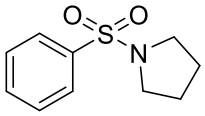
60% yield



53% yield



61% yield



65% yield

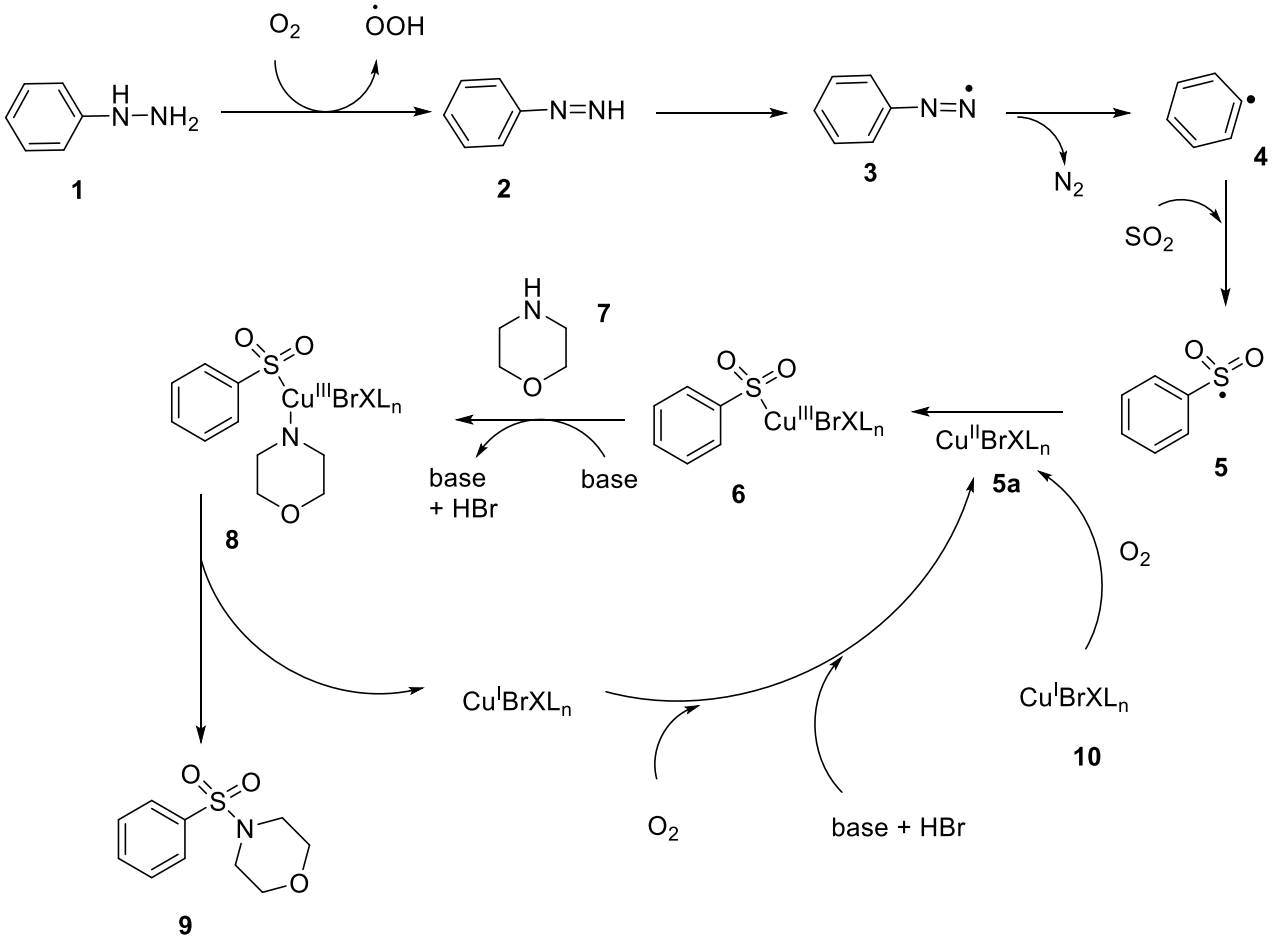
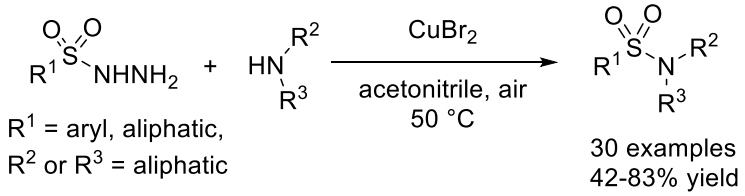


Figure 43. CuBr-$S(Me)_2$ catalyzed coupling of hydrazines with amines and DABSO to form sulfonamides

Sulfonamides were prepared by an ecofriendly benign process involving sulfonamides reaction from sulfonyl hydrazides and amines under moderate reaction conditions where water and nitrogen gas were librated byproduct. The desired products were synthesized with satisfactory yields, and mechanistic studies reveal thatradical sulfonyl formation was involved during the reaction process. The reaction cycle initiates with the reaction of Cu(II) species **1** with **2** to form intermediate **3**. In the following step, intermediate **3** reacts with amine **4** to form intermediate **5**. Finally, intermediate **5** to form final product **6** and subsequent regenration of catalyst (Figure 44).[90]



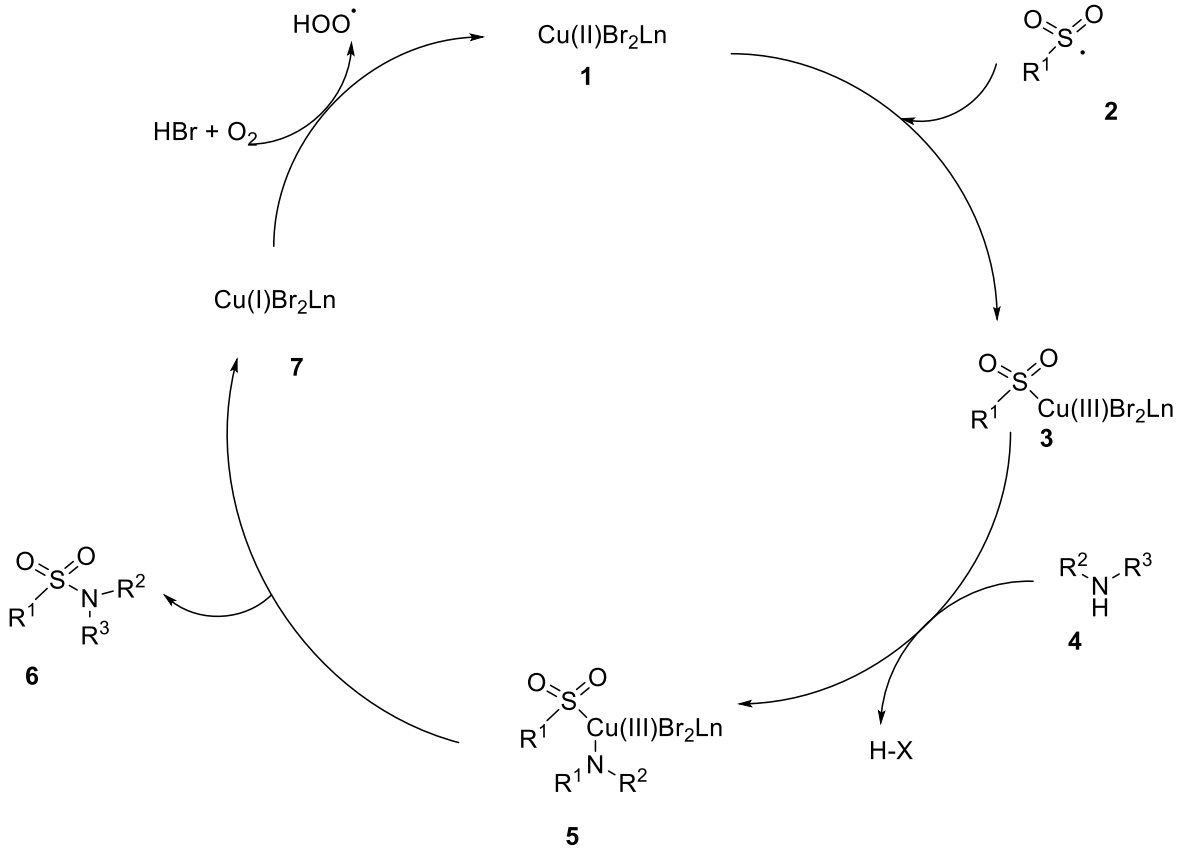


Figure 44. $CuBr_2$ facilitatedaerobic sulfonamides synthesis from sulfonyl hydrazides and amines

Copper(I)iodide/K_3PO_4 promoted the reaction of *N*,*N*‘-di(*p*-toluenesulfonyl)-1,2-diamine with 1-bromo-1-alkyne using DMF as a solvent at 110 °C to form *N*,*N*‘-di(*p*-toluenesulfonyl)-1,2,3,4-tetrahydropyrazines in satisfactory yields *via*a multistep process involving alkylation of diamine derivative with 1-bromo-1-alkyne followed by 6-*endo-dig* ring closure involving acetylenic bond with sulfonylamine moiety of the diamine. In the aforementioned reaction, replacing 1,2-diamine with *N*,*N*‘-di(*p*-toluenesulfonyl)-1,3-diamine or *N*-(*p*-toluenesulfonyl)-2-amino-1-ethanol resulted in the formation of seven-membered diazacycle or six-membered *N*,*O*-heterocycle (Figure 45) [91].

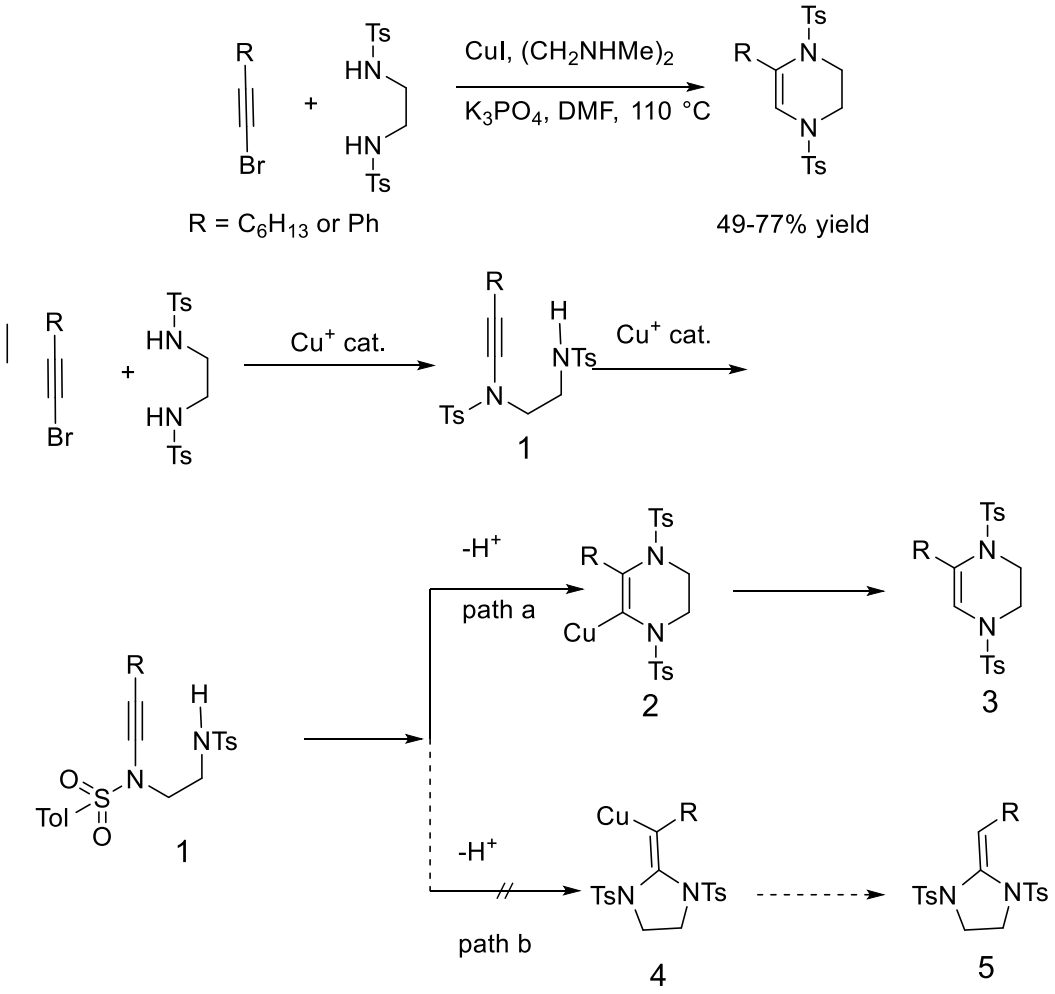


Figure 45. Copper(I)iodide/K_3PO_4 catalyzed synthesis of heterocyclic compounds using 1,2-double amination of 1-halo-1-alkynes

N-aryl amines are omnipresent organic compounds finding applications in pharmaceuticals, agrichemicals, material science and crop protecting chemicals. Clan, Evans and Lam separately first investigated copper mediated heteroarylation using arylboronic acid as th arylating source. However, these reactions are moslty performened using organic bases and diversity of organobornon compounds. [92] [93] [94] [95] Zheng and cowrkers have repored

application base free copper mediated N-arylation using arylboroxines and ethanol and solvent. A simple copper salt catalyzed N-arylation reaction with arylboronic acids has been reported for the coupling of arylboronic acids with imides was performed in MeOH to give *N*-arylimides in excellent yields; a variety of amines, amides and sulfonamides could also be successfully coupled with arylboronic acids to give corresponding N-arylated products in moderate yields (Figure 46).[96]

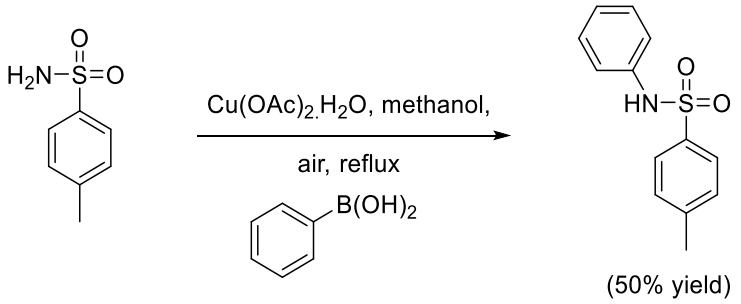


Figure 46. Copper-catalyzedN-arylation of sulfonamides with arylboronic Acids

Copper(I)iodide/Cs_2CO_3 based catalytic system provided an efficient protocol for the N-arylation of sulfonamides using DMF as a solvent at 130 °C under aerobic conditions. The desired N-arylation of sulfonamides was performed to generate the desired product with good to excellent yields (up to 91%) (Figure 47).[97]

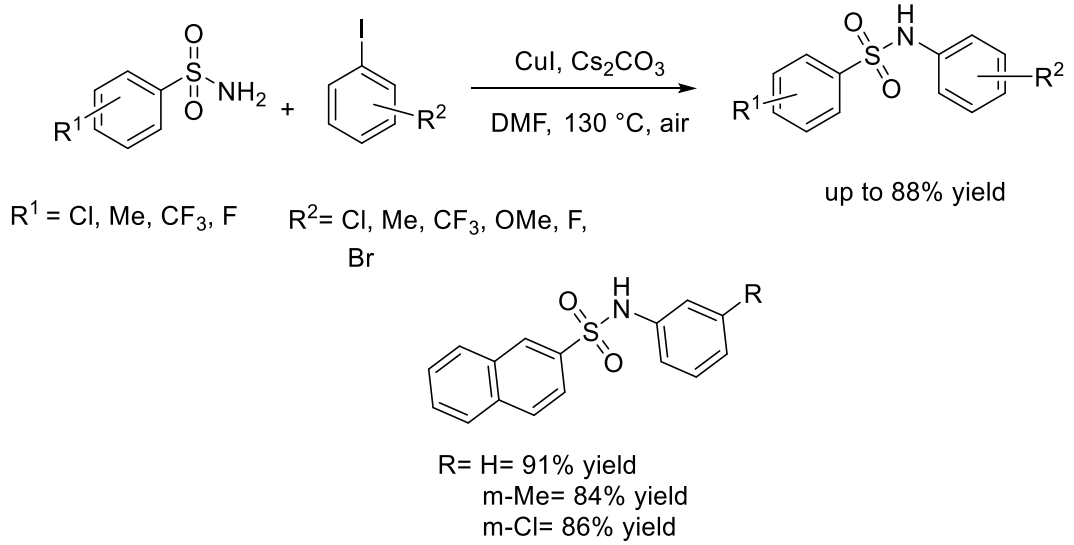


Figure 47. Copper(I)iodide/Cs_2CO_3N-arylation of sulfonamides

Copper(I)iodide (CuI)/*N*,*N*′-dimethylethylenediamine (DMEDA)/Cs_2CO_3 was used for the synthesis of *exo*or *endo*5-, 6-, 7-, and even 8-membered heterocyclic enamines by intramolecular C−N coupling with sulfonamides and vinyl halides. The heterocyclic amines

were formed in good to excellent yields via a facile process using 1,4-dioxane as a solvent at 100-150 °C (Figure 48).[98]

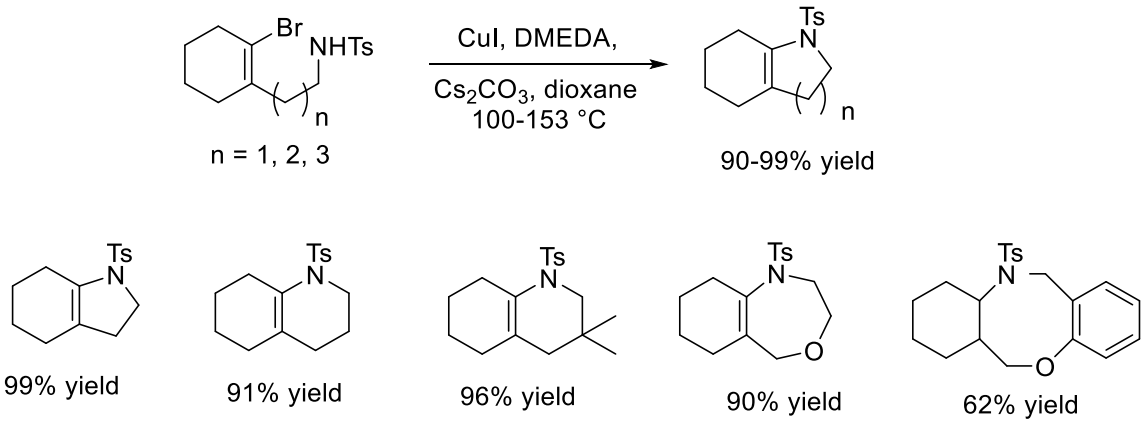


Figure 48. Copper(I)iodide (CuI)/*N*,*N*′-dimethylethylenediamine (DMEDA)/Cs_2CO_3synthesis of heterocyclic enamines and macrolactams

The organic molecules composed of 1,4-benzoxazines and phenoxazine moieties are important for chemists due to their biological applications. Copper(I)iodide/K_2CO_3 catalyzes *trans*-3,4-dihydro-2*H*-1,4-benzoxazine synthesis from aziridines and o-iodophenols. The catalytic reaction was performed in DMF at 110 °C via cascade process involving ring-opening of aziridine ring followed by reaction with *o*-iodophenols via copper-catalyzed Goldberg coupling cyclization involving intramolecular C(aryl)−N(amide) bond formation.The desired products were formed in good to excellent yields (Figure 49).[99]

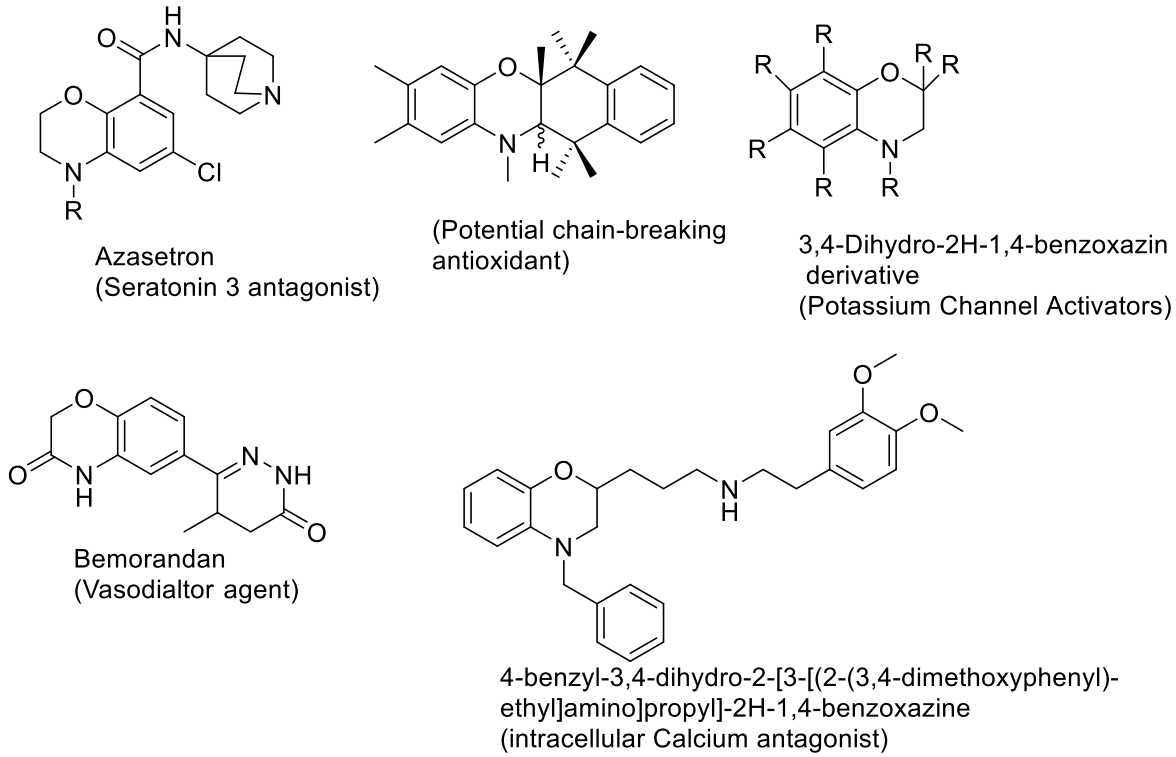


Figure 49. Bioactive 1,4-benzoxazine skeleton

Mechanism for the copper catalyzed 3,4-Dihydro-2*H*-1,4-benzoxazines starts with the base catalyzed deprotonation of 2-iodophenol (**1**) to form intermediate **2** followed by base catalysed aziridine S_N^2 ring opening and reaction with **2** to form intermediate **3**. In the subsequent step copper(I) catalyzed Goldberg coupling cyclization reaction starts with the reaction of intermediate **3** with Cu(I) **4** species to form intermediate species **5**. The intermediate **5** undergoes oxidative addition to form intermediate **6** followed by formation of byproduct and regeration catalyst (Figure 50).

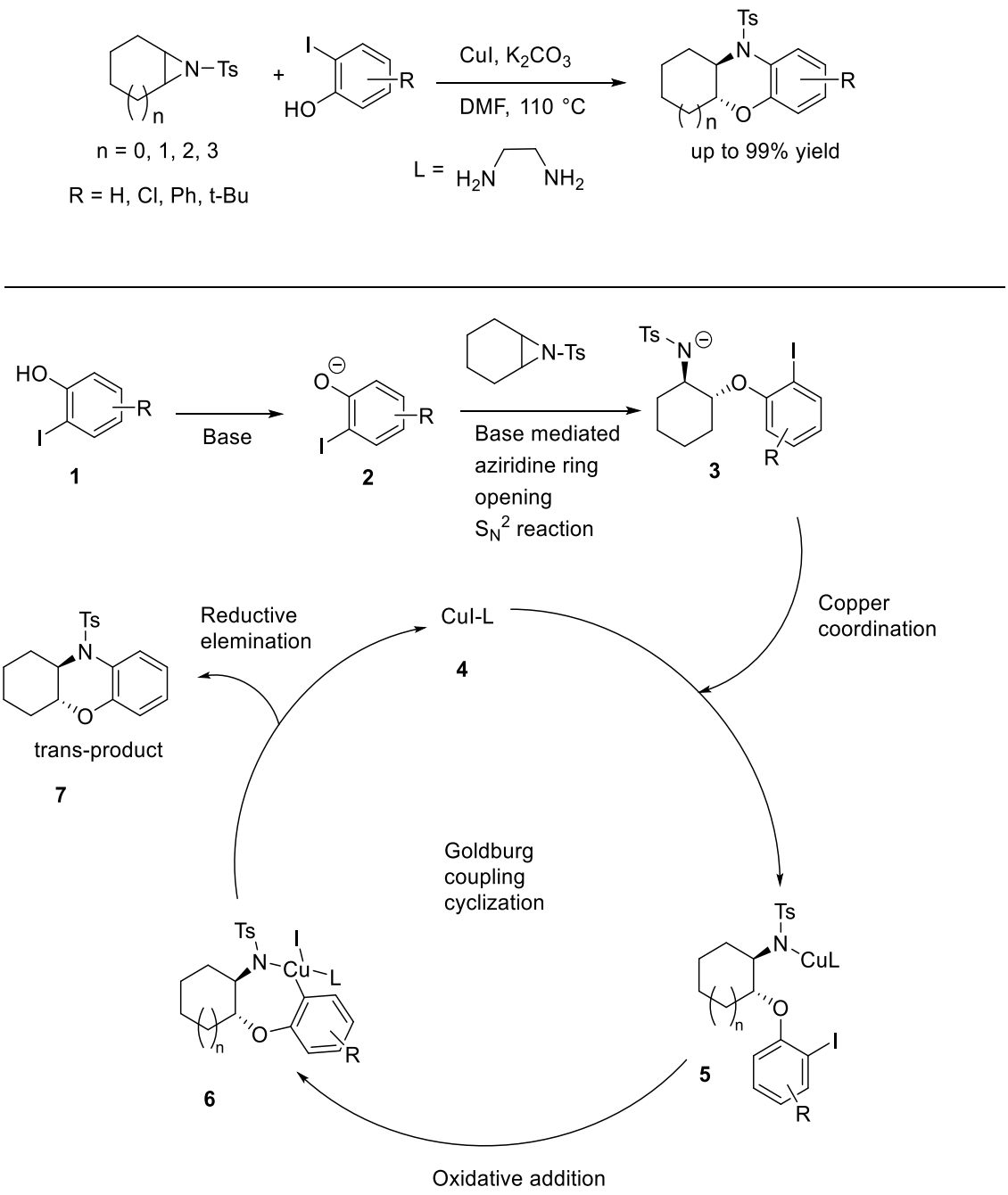


Figure 50. Copper(I)iodide/K_2CO_3 effectively promoted cascade process involving synthesis of 3,4-Dihydro-2*H*-1,4-benzoxazines

Copper triflate [$Cu(OTf)_2$]/Cs_2CO_3 promoted one-pot synthesis of sulfonamides composed of (hetero)aryl boronic acids, amines and DABSO reagent as sulfur dioxide surrogate at 130 °C using DMSO as a solvent. The catalytic system was adequate for a variety of (hetero)aryl boronic acidslike aryl, heteroaryl and alkenyl boronic acids, and amines cyclic and acyclic alkyl secondary amines, and primary anilines (Figure 51).[100]

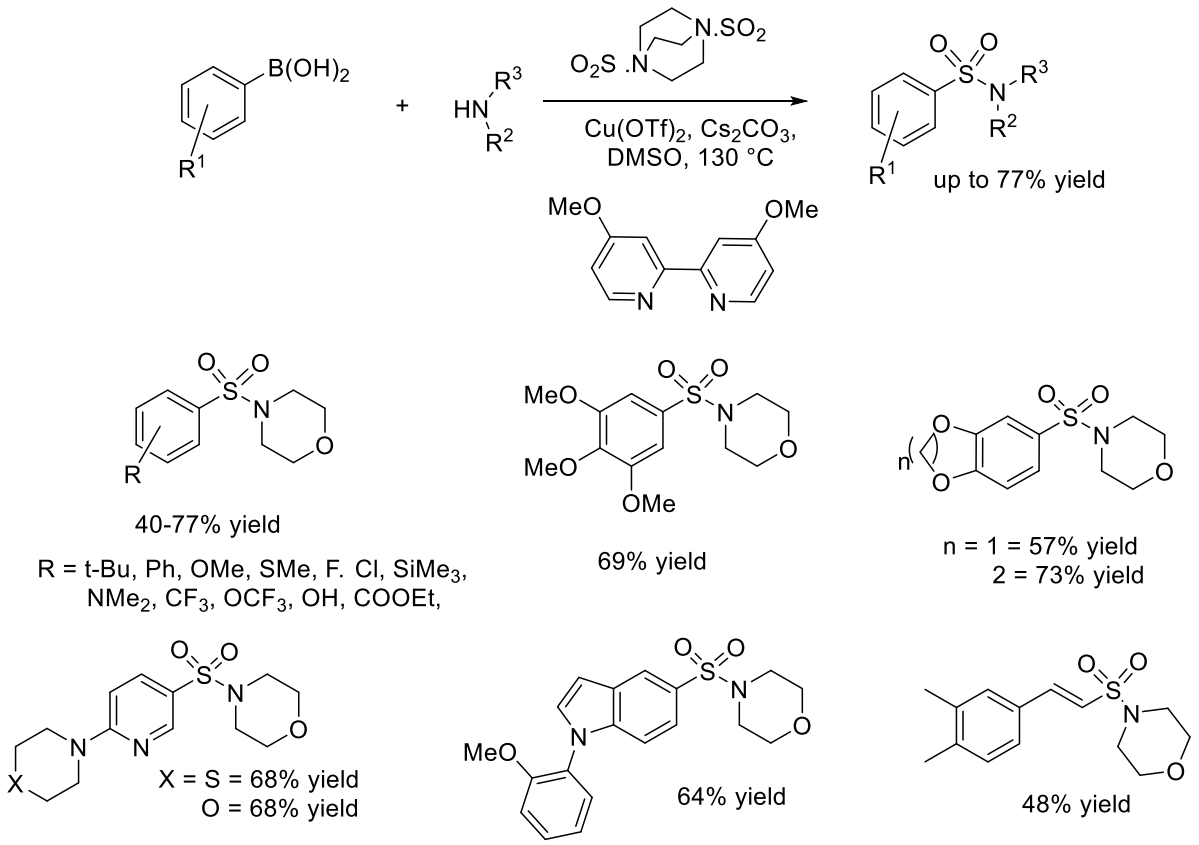


Figure 51. Copper triflate [$Cu(OTf)_2$]/Cs_2CO_3 promoted sulfonamides synthesis by multicomponent synthesis

Copper(I)iodide/1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) catalyzed amidation of arylboronic acid with $TsNBr_2$ as the nitrogen source at room temperature. A variety of arylboronic acids were effectively transformed to the corresponding *N*-arylsulfonamide derivatives (Figure 53).[101]

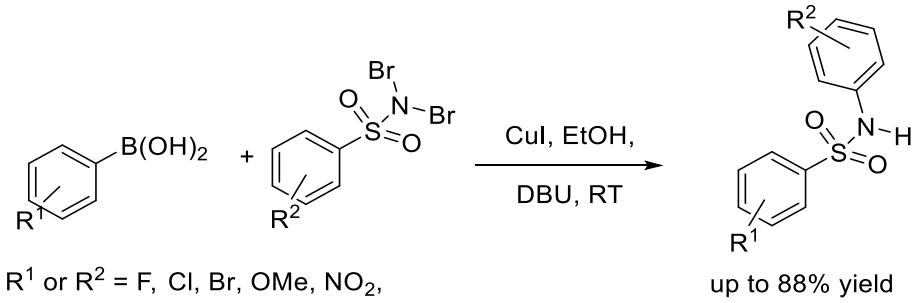


Figure 52. CuI catalyzed sulfamidation of arylboronic acid using $TsNBr_2$ at room temperature

$Cu(OAc)_2$ was used as an efficient catalytic material for C-H bond activation of 2-phenylpyridine with amides resulting in N-substituted amides. The catalytic system tolerates broad substrate scope resulting in the formation of variety of nitrogen reagents like sulfonamides, carboxamides, and anilines in moderate to good yields (Figure 52).[102]

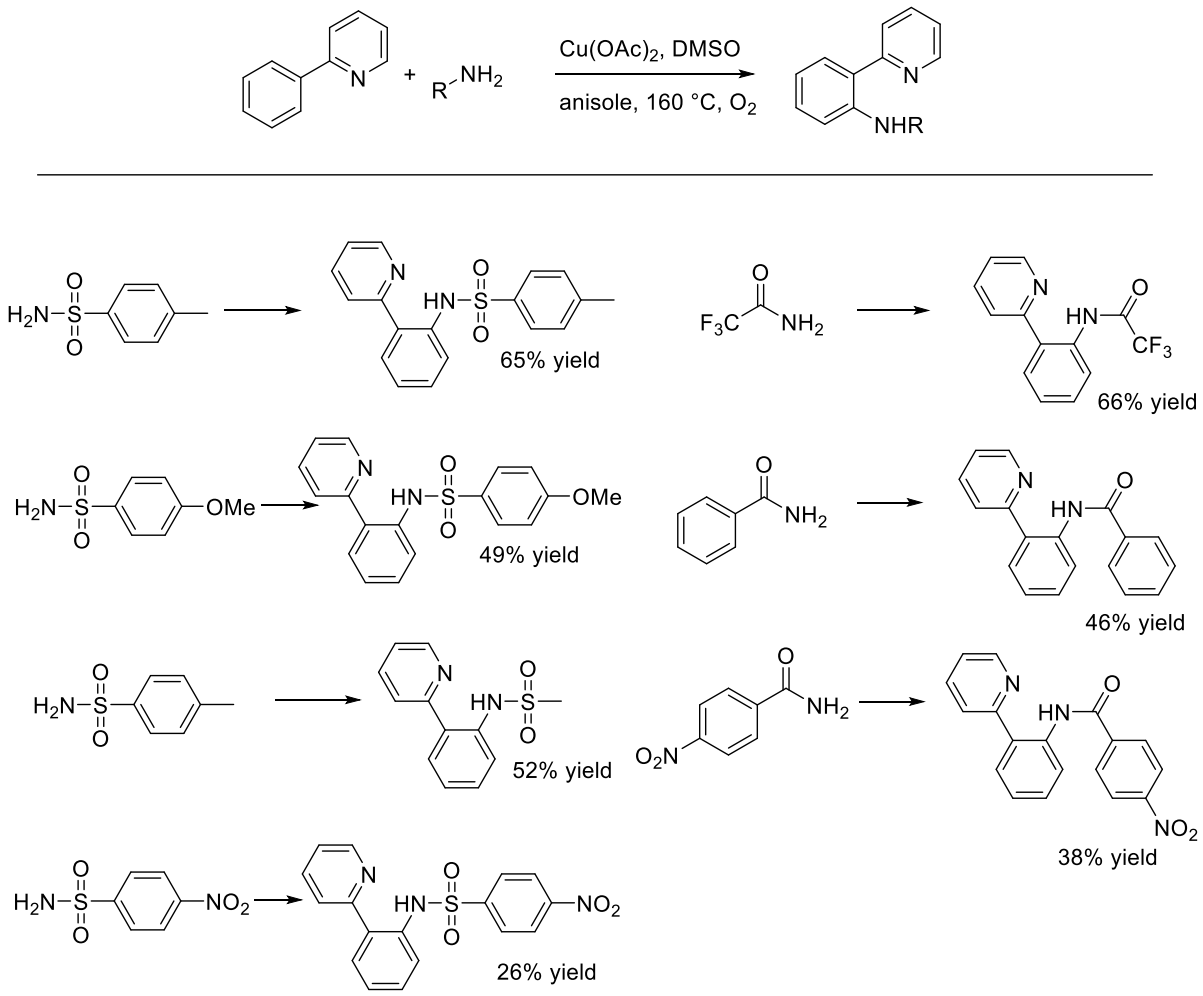


Figure 53. $Cu(OAc)_2$/DMSO promoted amidation of 2-phenylpyridine using molecular oxygen as the terminal oxidant

The catalytic cycle for the N-substituted amides synthesis of starts with the formation of intermediate **4** by the reaction of **1**, **2** and **3**. In the following step, the intermediate **4** reacts with **5** to form intermediate **6** folllowed by oxidation to form intermediate **7**. Finally, the intermediate **7** rearranges to form final product **8** and regeration of catalyst (Figure 54).

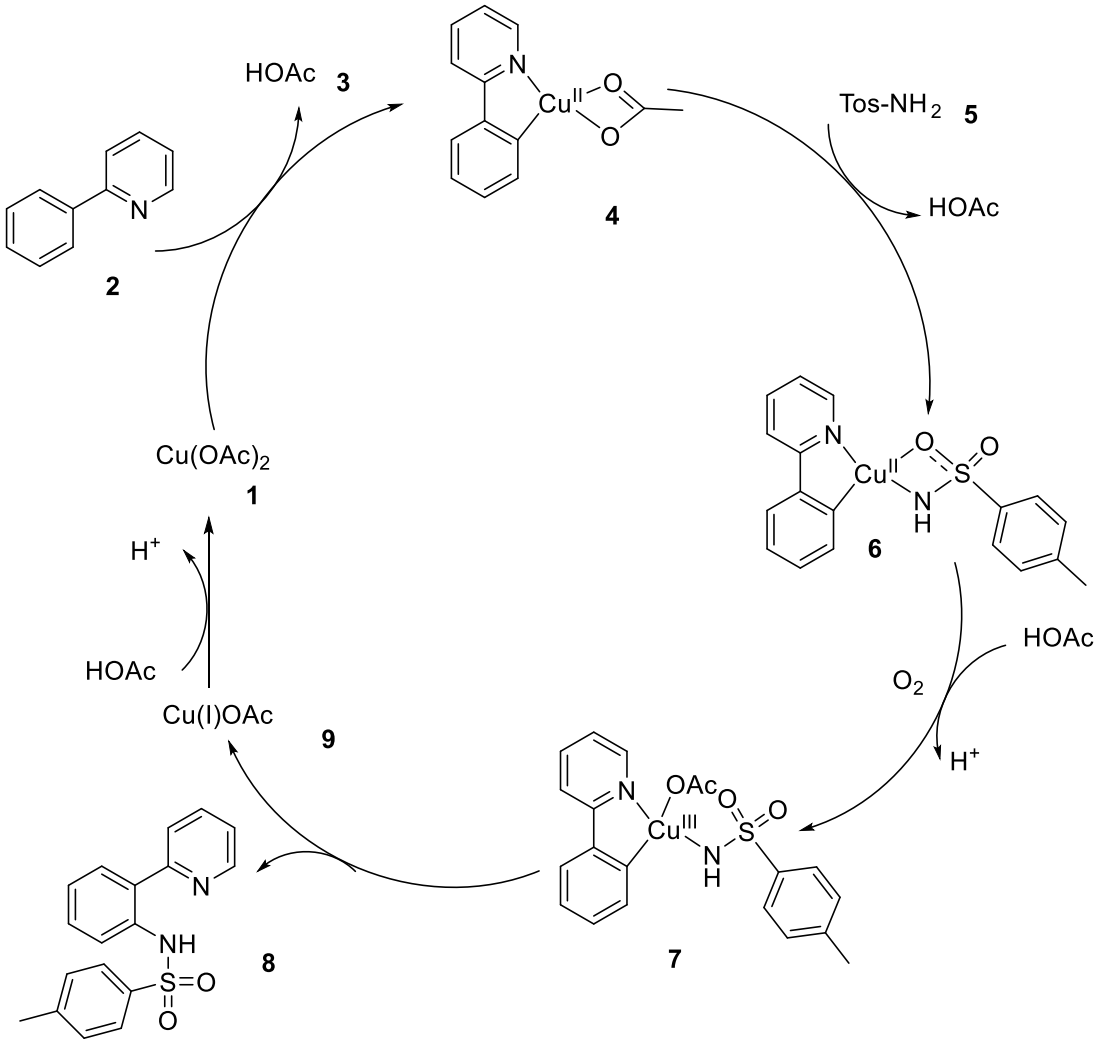
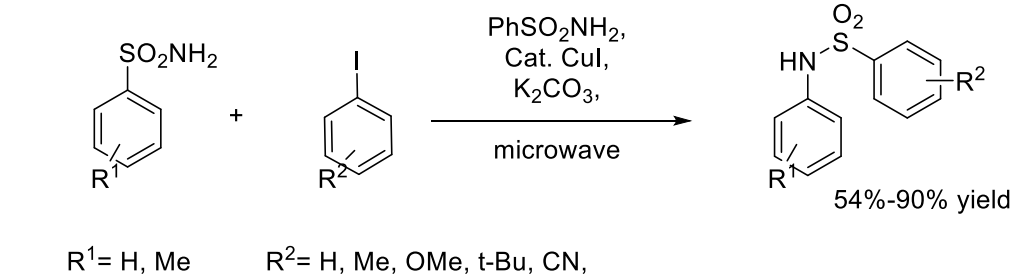


Figure 54. Mechanism for the copper catalysed sulfonamide synthesis via amidation of 2-phenylpyridine

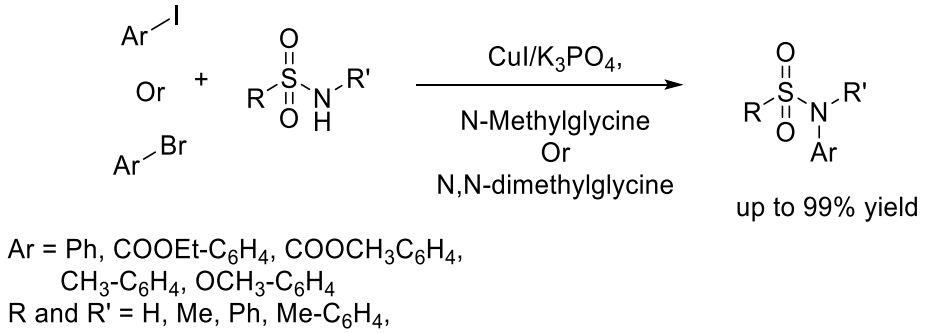
Copper(I)iodide/K_2CO_3 was used as the catalytic material for the *N*-arylation of sulfonamides with a broad range of aryl bromides and iodides. The reaction was performed under microwave conditions yielding N-arylated sulfonamide with promising yields (Figure 56).[103]



R^1= H, Me R^2= H, Me, OMe, t-Bu, CN,

Figure 56. CuI/K_2CO_3 catalyzed synthesis of *N*-arylation of sulfonamides with aryl bromides or iodides under microwave conditions

CuI/K_3PO_4 catalyzes N-alkylation of sulfonamides with aryl halides (X= I or Br) using *N*-methylglycine (for aryl iodides) or *N*,*N*-dimethylglycine (for aryl bromides) as a ligand. In the reaction system, K_3PO_4 was used as a base, and the reaction was performed under facile reaction conditions generating the desired N-alkylation of sulfonamides in good to excellent yields. Mechanism for the N-alkylation of sulfonamides synthesis involves oxidative addition, reductive elemination and ligand exchange reaction as shown in the figure 58.[104]



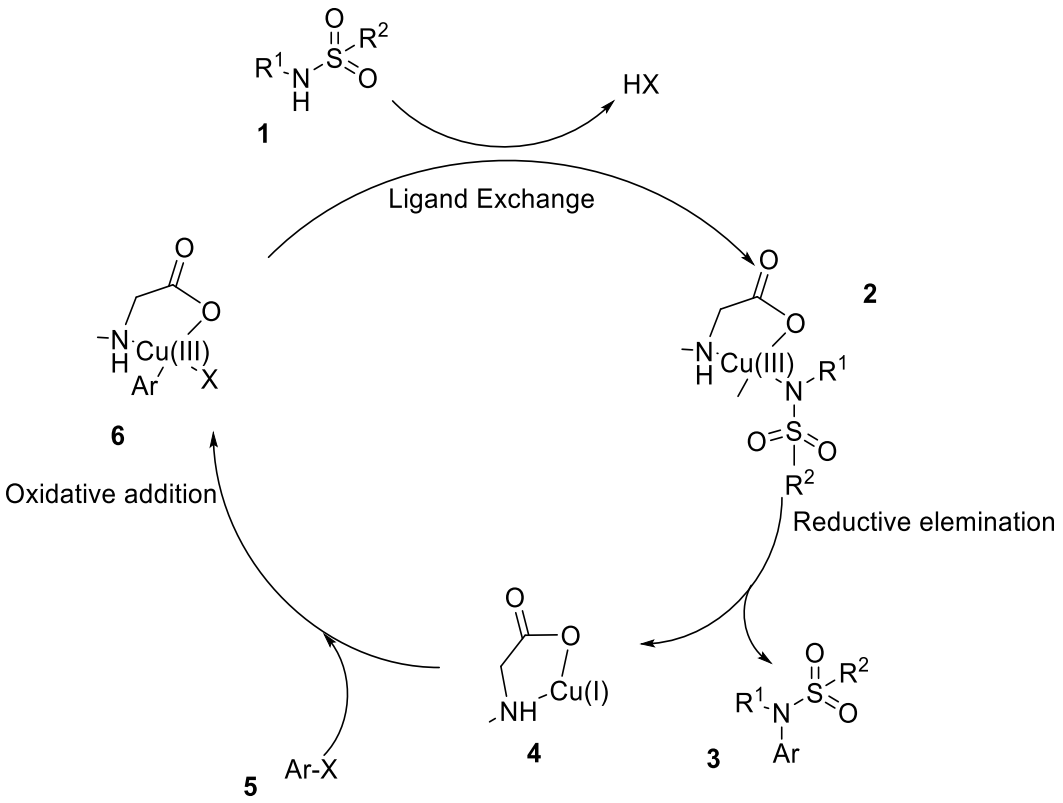


Figure 58. CuI/K_3PO_4 catalyzed synthesis of N-alkylated sulfonamides from sulfonamides and aryl halides

$Cu(OAc)_2.H_2O/K_3PO_4$ was used as the catalyst for the $C(sp^2)$-H activation followed by $C(sp^2)$-N bond formation by dehydrogenative coupling followed by N−H sulfoximines

followed by C−N bond formation under ambient conditions and aerobic conditionsto form the corresponding *N*-arylsulfoximines in satisfactory to high yield (Figure 59).[105]

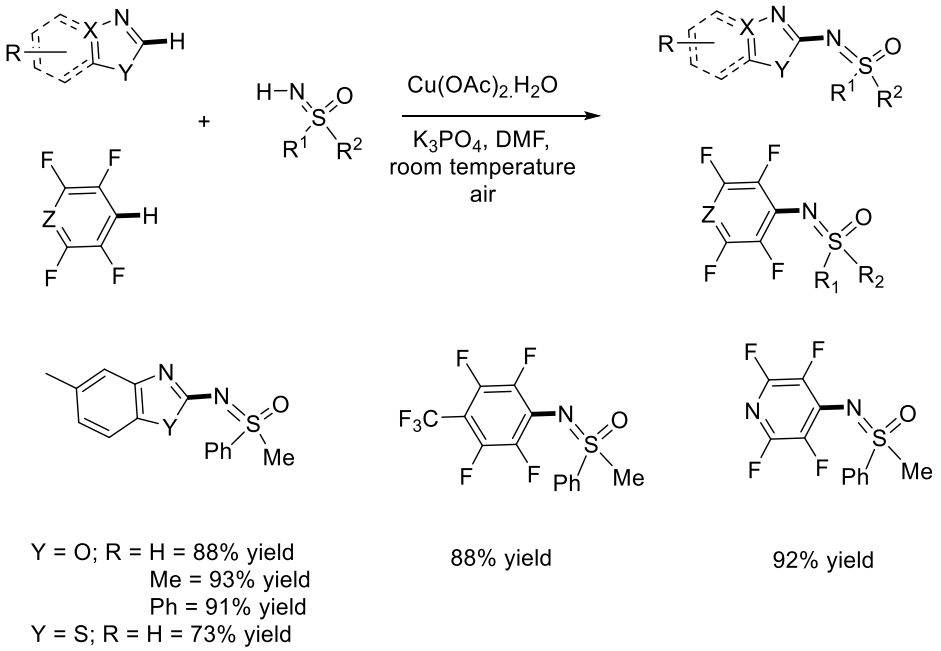


Figure 59. $Cu(OAc)_2.H_2O/K_3PO_4$ promoted sulfoximination of azoles and polyfluoroarenes at room temperature

Copper(I) oxide was used as the catalyst for the synthesis of sulfonamides by reacting sulfonyl chlorides with triethylamine under moderate conditions and in oxygen environment. The catalytic reaction performed using 1,2-dichloroethane as a solvent. The reaction proceeded by C–N bond cleavage of tertiary amines under aerobic conditions yielding the desired sulfonamideswithsatisfactory yields. The mechanism for the copper catalysed sulfonyl chlorides reaction with triethylamine initiates with the oxidation of **1a** with molecular oxygen to form intermediate **1b** followed by reaction of triethylamine **1c** to form intermediate **2**. In the subsequent step, intermediate **2** reacts with molecular oxygen to form intermediate **4** and acetaldehyde **3**. The intermediate **4** reacts with TsCl (**5**) results in the formation of byproduct **6** and regenration catalyst (Figure 60).[106]

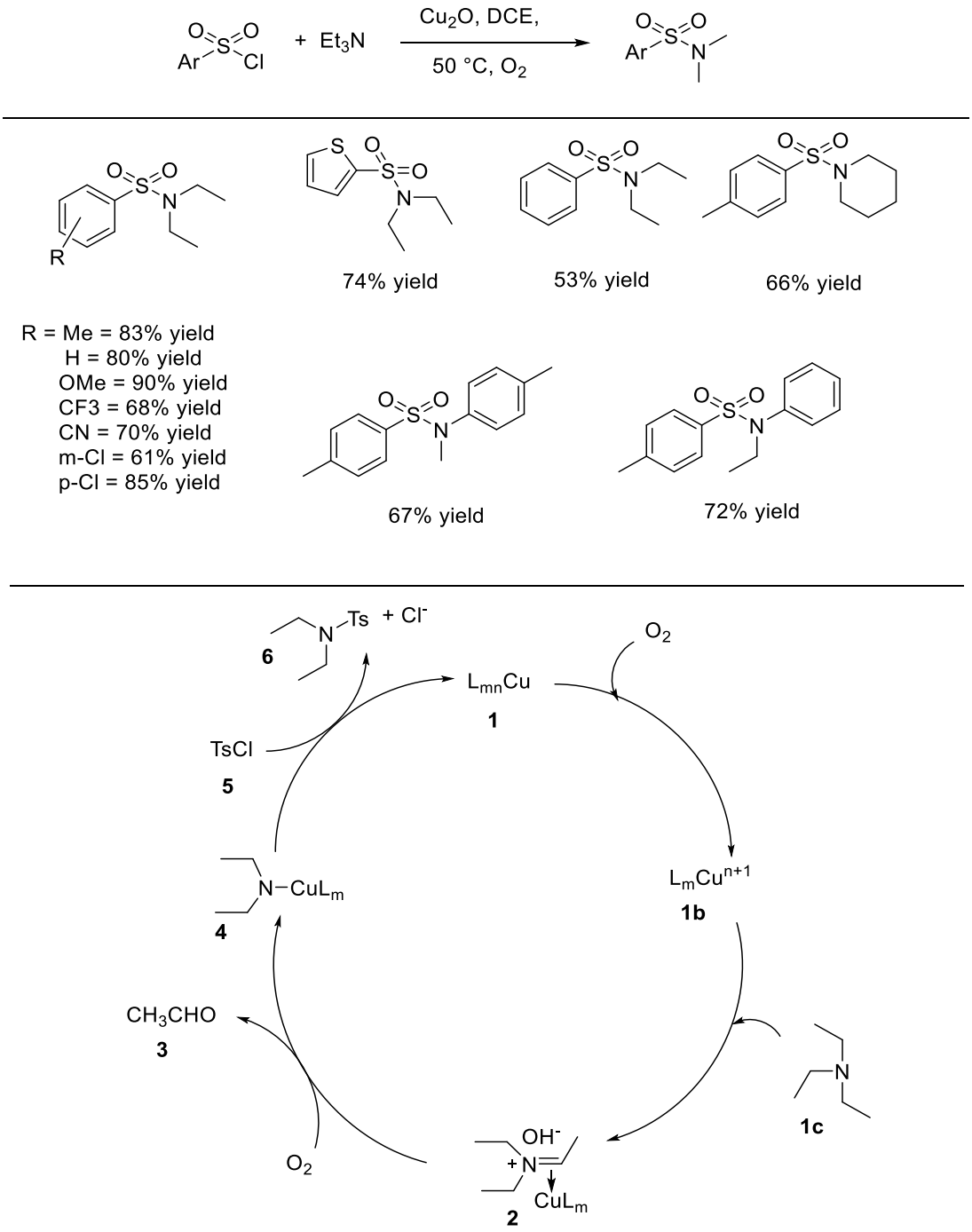


Figure 60. Cu_2O catalyzed synthesis of sulfonamides byreacting sulfonyl chlorides with triethylamine

Copper(I)iodide in corroboration with 1,3-di(pyridin-2-yl)propane-1,3-dione and K_2CO_3 enables the synthesis of *N*-(3-Pyridinyl)-substituted secondary and tertiary sulfonamides from 3-bromopyridine with primary and secondary alkyl and aryl sulfonamides($R^1NHSO_2R^2$·R^1 = H, Me, alkyl; R^2 = alkyl and aryl). The catalytic system also promoted coupling of sulfonamides with a variety of 2-Bromopyridine, 4-bromopyridine and substituted phenyl bromides under the mentioned reaction conditions (Figure 61).[107]

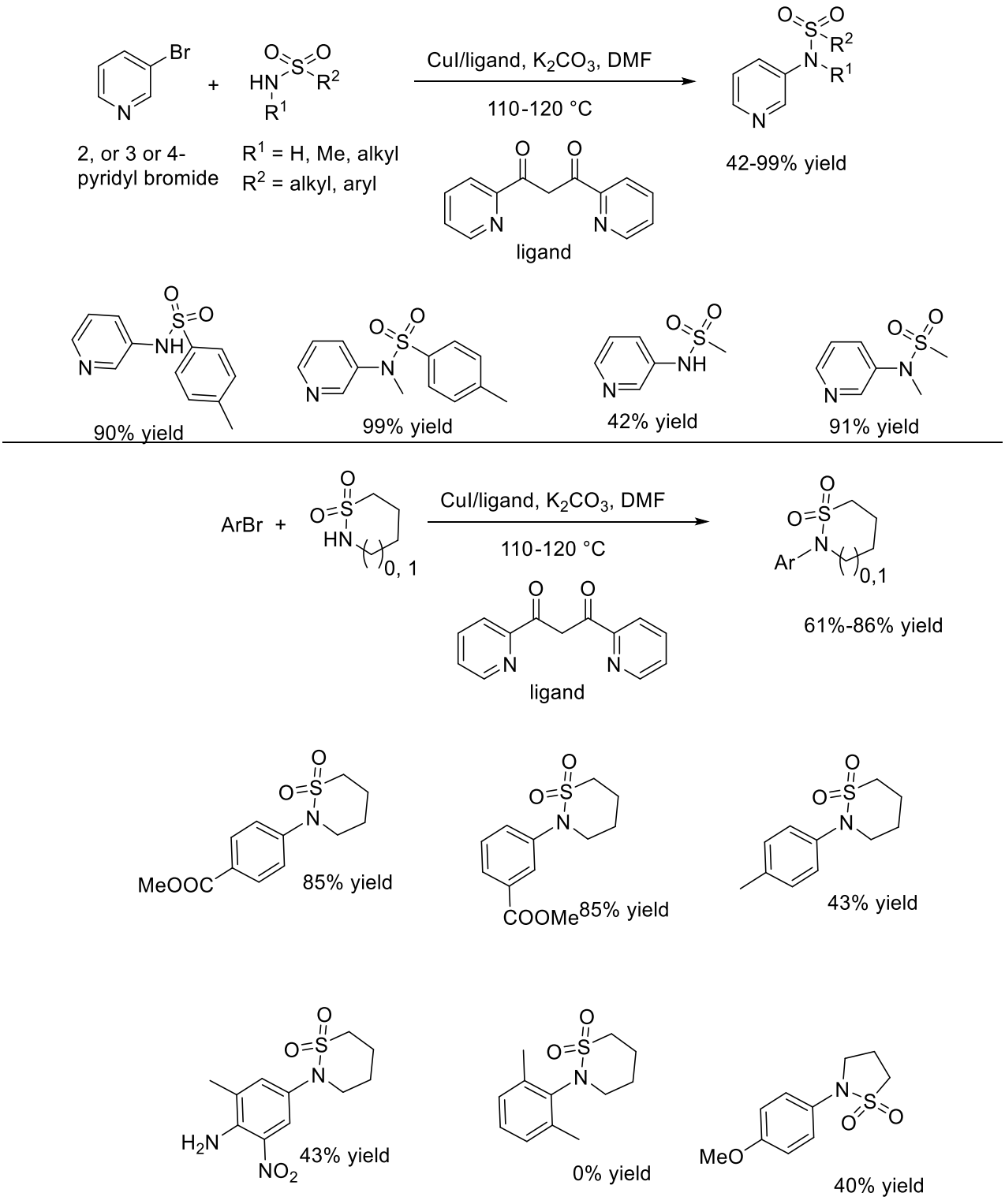


Figure 61. Copper(I)iodide/1,3-di(pyridin-2-yl)propane-1,3-dione/K_2CO_3 promoted cross coupling of 3-bromopyridine and sulfonamides

Copper(I)iodide/K_2CO_3 /N,N-dimethylethylene diamineeffectively promoted the N-arylation of sulfonamides with aryl halides under ambient conditions. The reaction medium

effectivelycatalyzedthe reaction of a variety of sulfonamide (alkyl or aryl) with a variety of heteroaryl bromides,including 2-bromothiazole in good to excellent yields (Figure 62).[108]

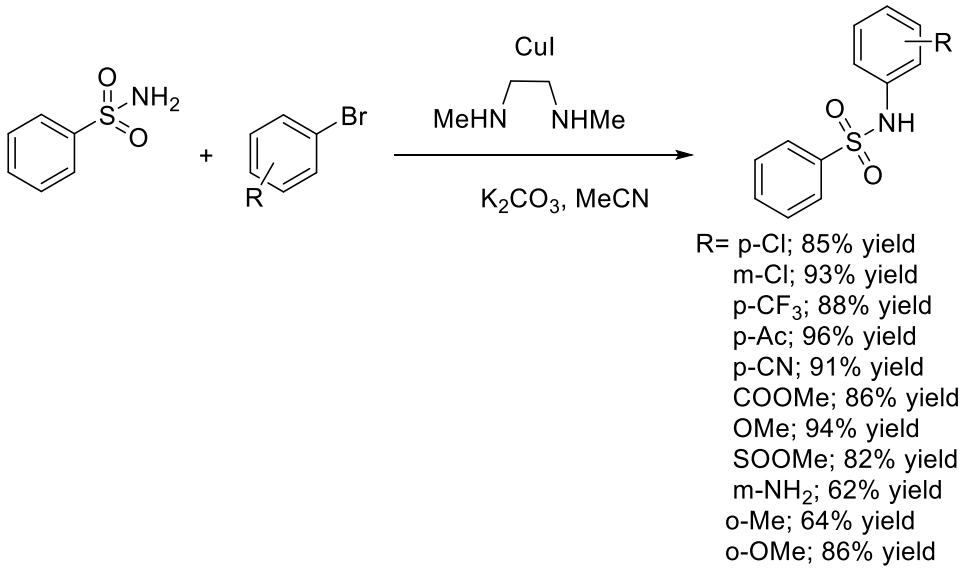


Figure 62. Copper(I)iodide/K_2CO_3 /N,N-dimethylethylene diamine catalyzes synthesis of N-arylation of sulfonamides by reacting sulfonamides with aryl bromides

Copper iodide catalyzes amidation of heterocycles (X=S, O, NR) with *N*-fluorobenzenesulfonimide (NFSI). Copper iodide catalyzed amidation involves C–H bond activation and C-N bond formation process leading to the synthesis of various α-amidated heterocycle derivatives with good to excellent yields. The proposed mchanism for the N-alkylated sulfonamides involves the formation of the Cu(I), Cu(II) and Cu(III) compexes. In the reaction NFSI promotes the oxidation of CuI to Cu(III) species **A**. Furthermore, the heterocyclic compounds interacts with the **A** to form Cu(II) intermediate **B** and the generation of heterocycle radical **C**. In the final step the heterocycle radical **C** gets oxidized by species **B** to form the amidated heterocycle product. (Figure 63). [109]

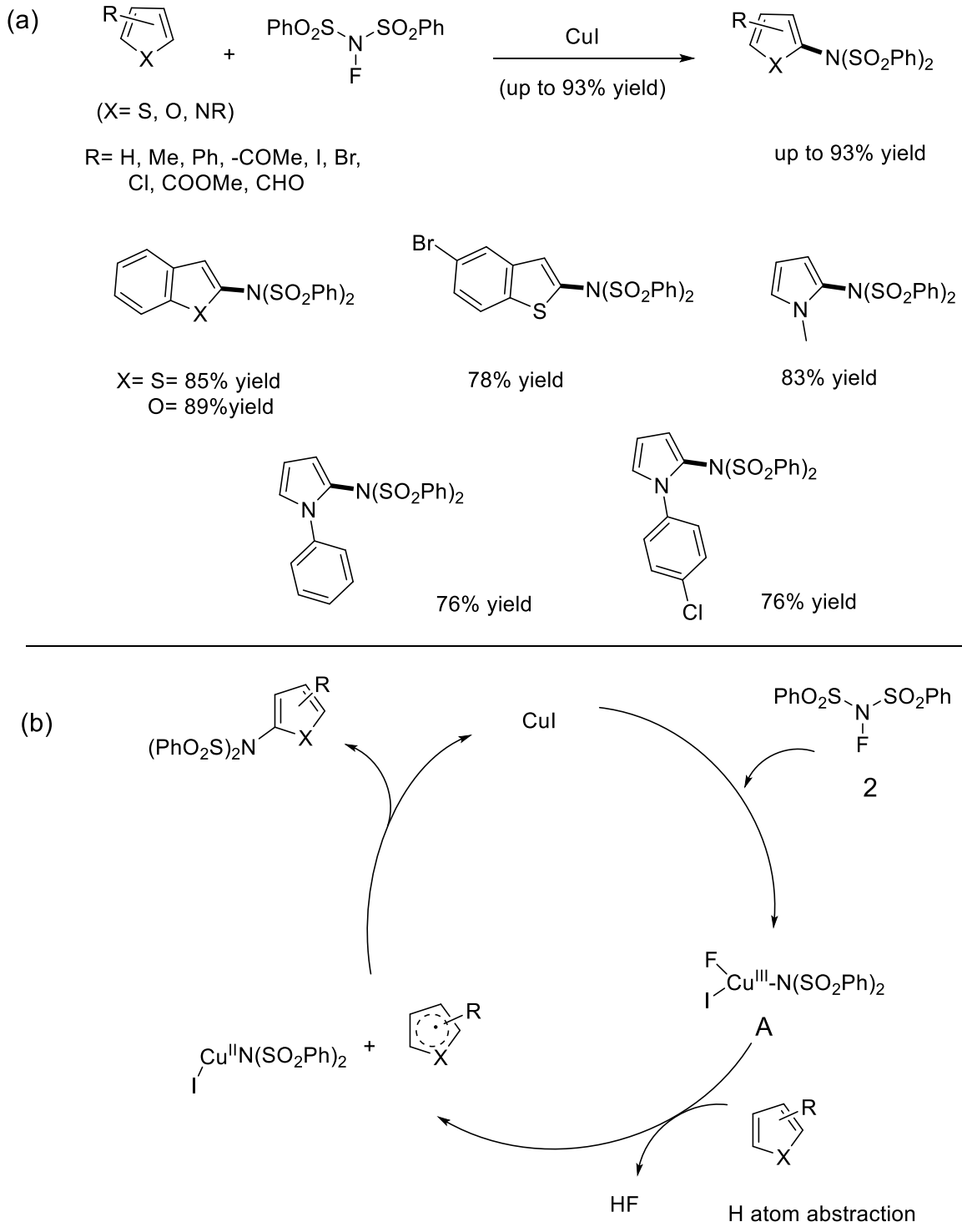


Figure 63 (a) CuI/NFSI effectivelycatalyzed amidation of heterocycles, (b) mechanistic pathway for the synthesis of α-amidated heterocycles

Copper(I) iodide/ K_2CO_3 facilitated the coupling of primary sulfonamides with a broad range of halogenated heterocyclic, including 2-heteroaryl halides. The catalytic reaction facilitated

by a diamine based ligand system using DMF as a solvent at 110 °C forming mono-*N*-heteroaryl sulfonamides(Figure 64)[110].

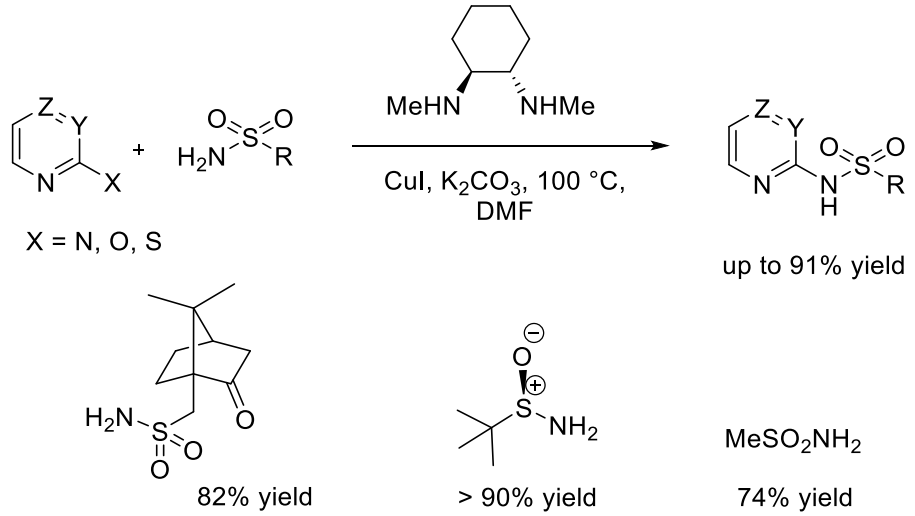


Figure 64. CuI/K_2CO_3 catalyzed *N*-heteroarylation of primary sulfonamides resulting in the formation of mono-*N*-heteroaryl sulfonamides

Copper powder/PhSH/$BF_3.OEt_2$ permits enables facile ring-opening reaction of 2-(2-haloaryl)-3-alkyl-*N*-tosylaziridines with thiophenol, resulting in the formation of 2-alkyl indoles with good yields. The reaction proceeds through regioselective ring-opening and subsequent intramolecular C–N cyclization. Mechanism for the copper catalyzed 2-alkyl indoles synthesis involves the reaction aziridine (**1**) ring opeing in the presence of thiol and $BF_3.OEt_2$ to form intermediate **2**. In the next step, **2** in the presence of copper powder undergoes cyclization to form intermediate **3**. In the sucessive steps intramolecular rearragements to form final product **6** and catalyst regernation occcurs. (Figure 65).[111]

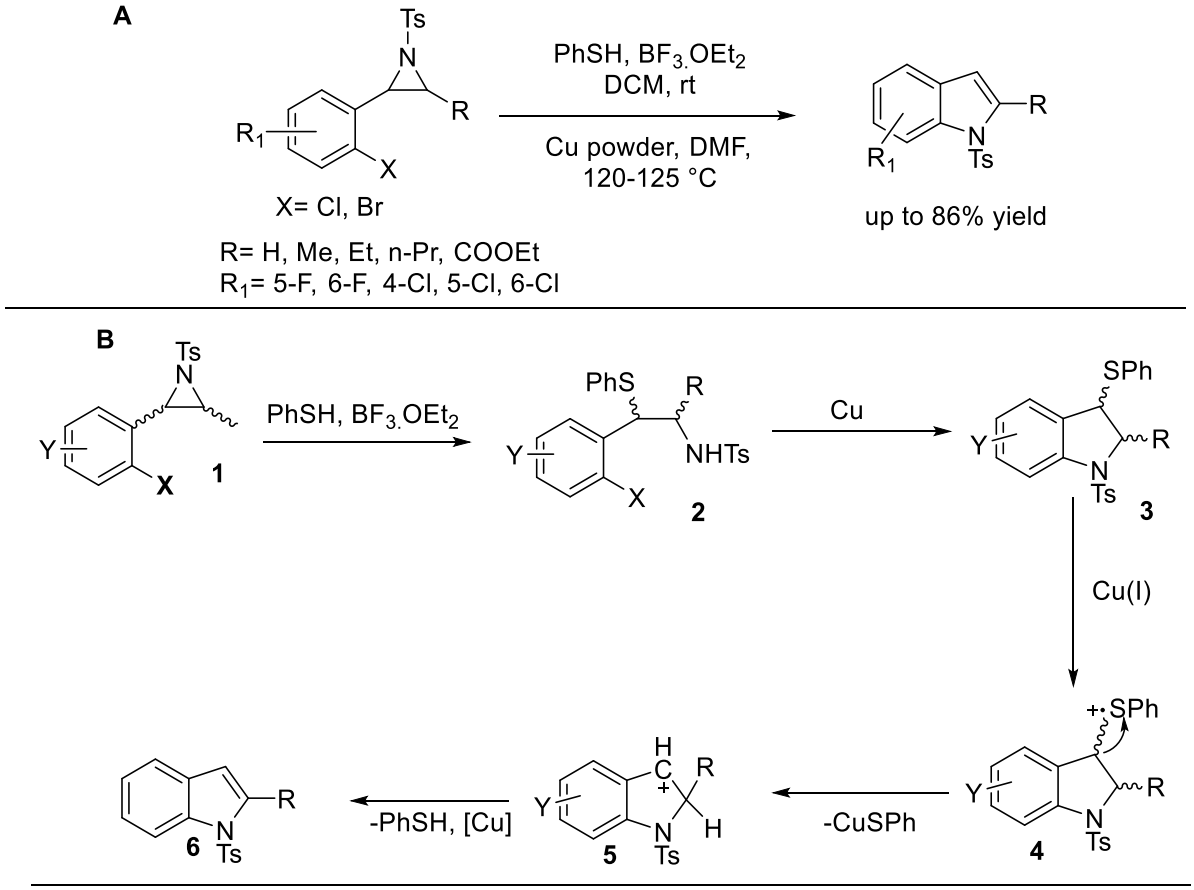


Figure 65. Copper powder/PhSH/BF_3.OEt_2 catalyzed synthesis of 2-carboxyindole

Copper(II)bromide/PPh_3 effectively promoted transsulfinamidation of the secondary or tertiary sulfinamides of primary sulfinamides with *O*-benzoyl hydroxylamines under moderate reaction conditions using argon gas. Alternatively, when the catalytic reaction was performed with*N*-aryl sulfinamides and *O*-benzoyl hydroxylamines using copper(I)bromide as the catalyst, the desiredproduct *N*-aryl sulfonimidamides wasobtained in moderate to satisfactory yields at 80 °C using acetonitrile as a solvent under inert atmosphere (Figure 66).[112]

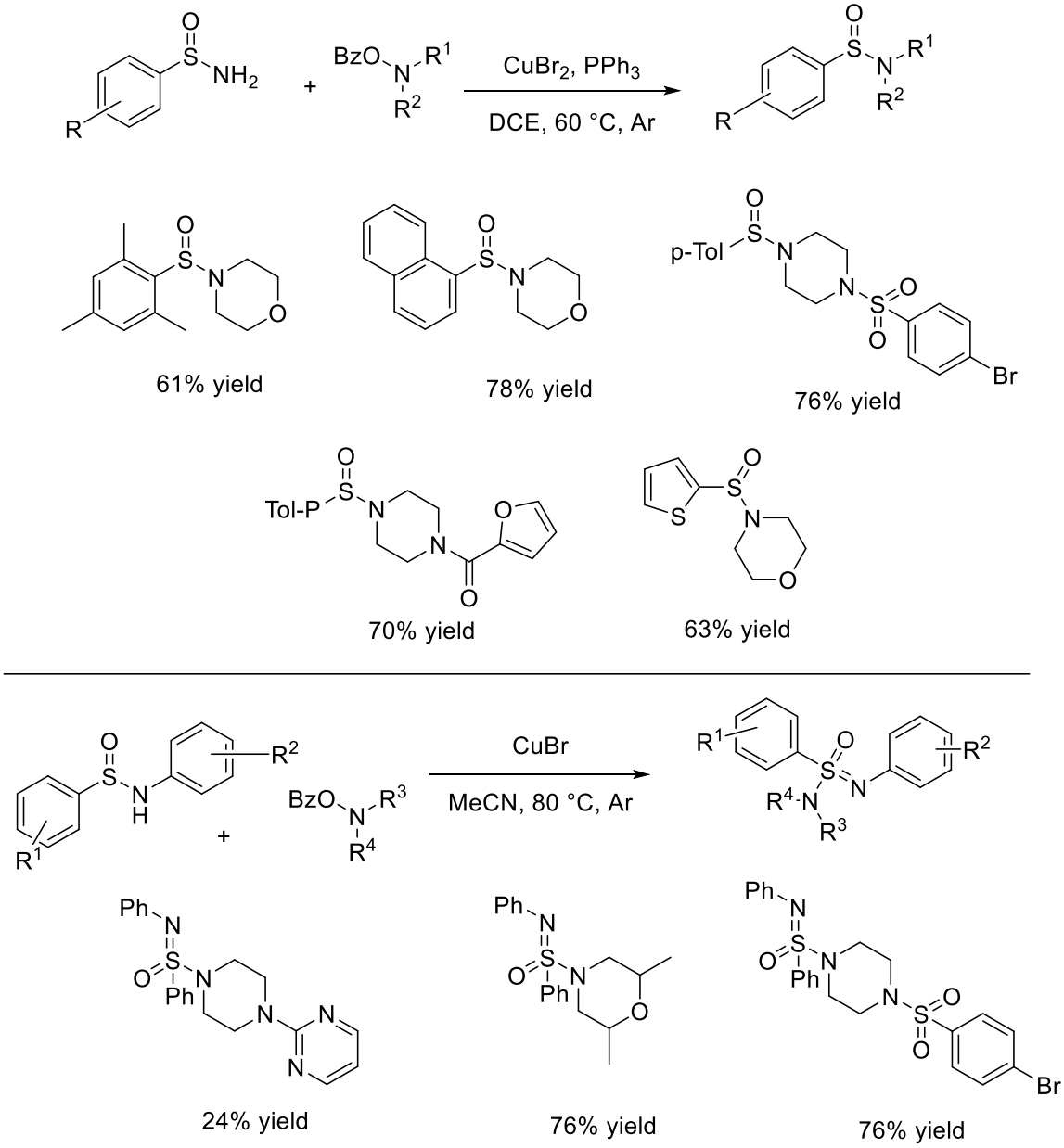


Figure 66. Transsulfinamidation of sulfinamides promoted by copper catalysts for sulfonamides and sulfonimidamides

Mechanism for the transsulfinamidation initiates by the reduction of Cu(II) to Cu(I) species. The resulting Cu(I) species further gets oxidized to Cu(III) by O-benzoylhydroxylamine and formation of intermediate **A**. The resulting intermediate **A** reacts with sulfinamides leads to the formation of intermediate **B**. The intermediate **B** in the subsequent steps converts to **C** *via* the migration of the metallic component from nitrogen to sulfur. The resulting produt **C** reductively eliminates the Cu(I) to complete the catalytic cycle and generating the desired N-arylated sulfonimidamide and labile unsubstituted product (See Figure 67).

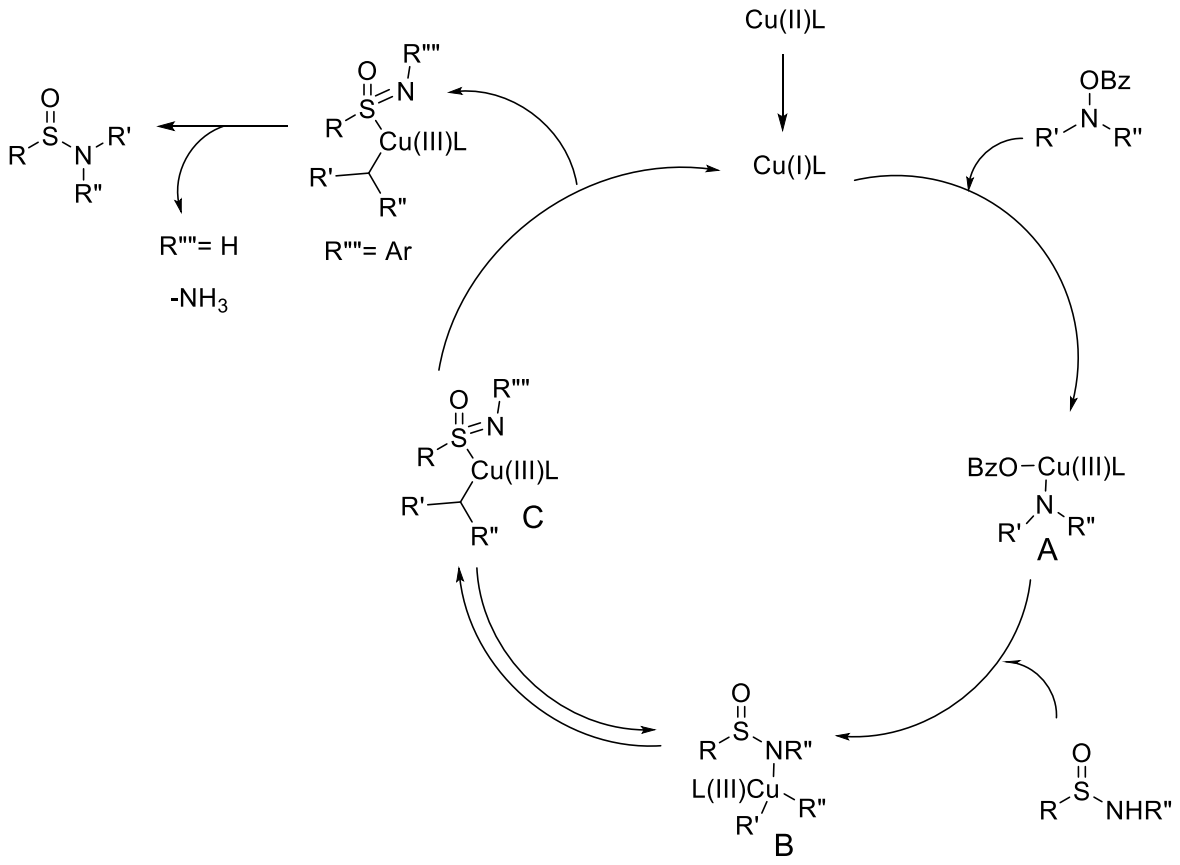


Figure 67. Mechanism for the copper catalysed N-aryl sulfonimidamides

2.4. Sulfonamide synthesis by N-X (heteroatom) bond activation

Copper(II)bromide promoted efficient amination of sodium sulfinates using *O*-benzoyl hydroxylamines as amine sources under ambient reaction conditions using dichloroethane as a solvent. The catalytic system enables the amination of a variety of sodium sulfinates using *O*-benzoyl hydroxylamines in good to excellent yields without using any ligand in the reaction system. Mechanism for the aformentioned reaction initates with the reaction of R-SO_2Na with copper(I) bromide (**9**) to form intermediate **1**. The intermediate **1** reacts with *O*-benzoyl hydroxylamines **2** to form intermediate **3**. Thereafter, intermediate **3** reforms to form final product and subsequent regeneration of product (Figure 68).[113]

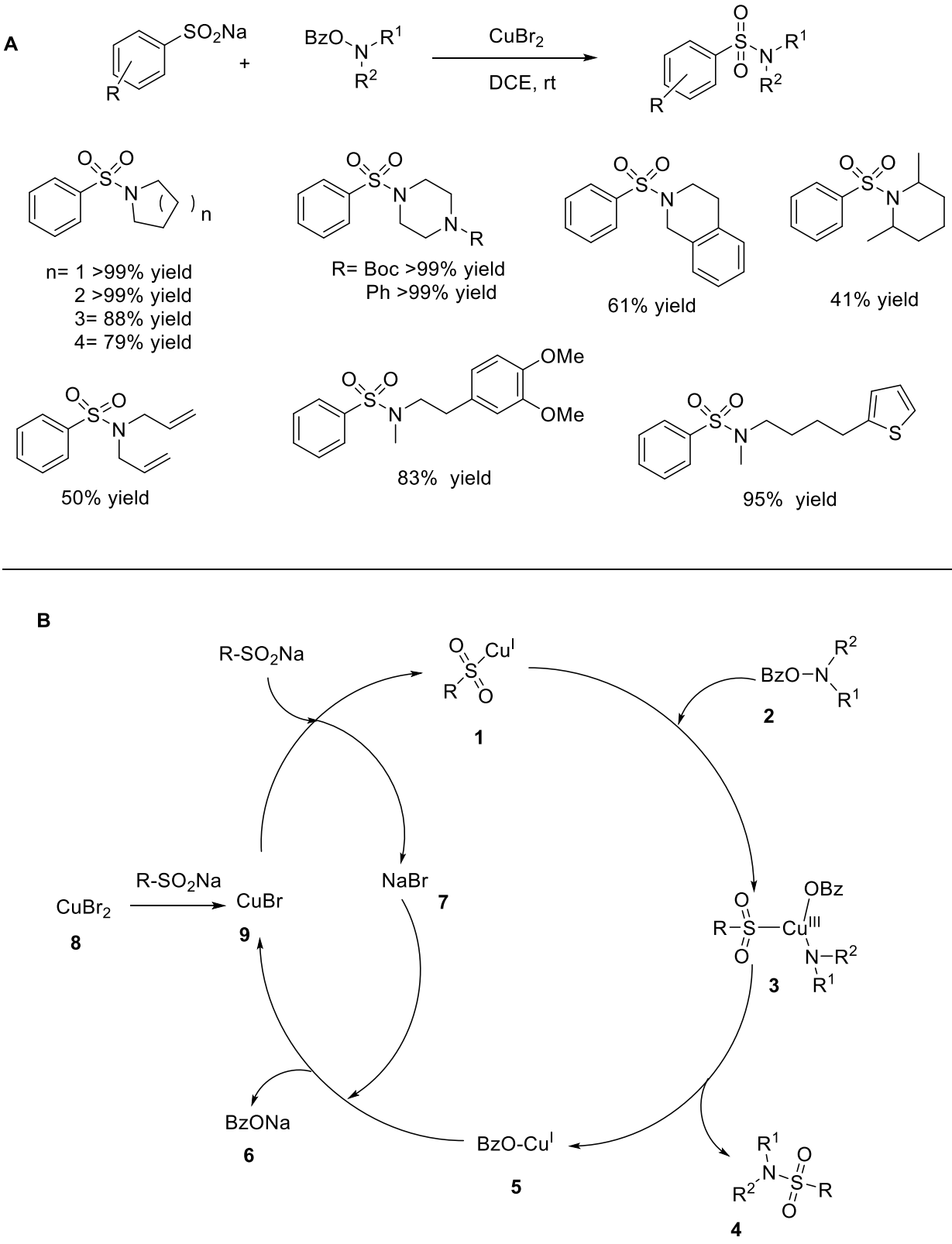


Figure 68. $CuBr_2$promoted amination of sodium sulfinates with *O*-benzoyl hydroxylamines under ambient conditions

$Pd(OAc)_2/Cu(acac)_2$ effectively catalyzed synthesis of 8-(arylsulfonyl)methylamino-7-deazapurines or to 7-chloro-8-(arylsulfonyl)methylamino-7-deazapurines by reacting *N*-chloro-*N*-alkyl-arylsulfonamides with 7-deazapurines. The catalytic reaction proceeded by C–H amination or C–H chloroamination of 7-deazapurines under ambient conditions using bipyridine as ligand and Na_2CO_3 as a base (Figure 69) **[114].**

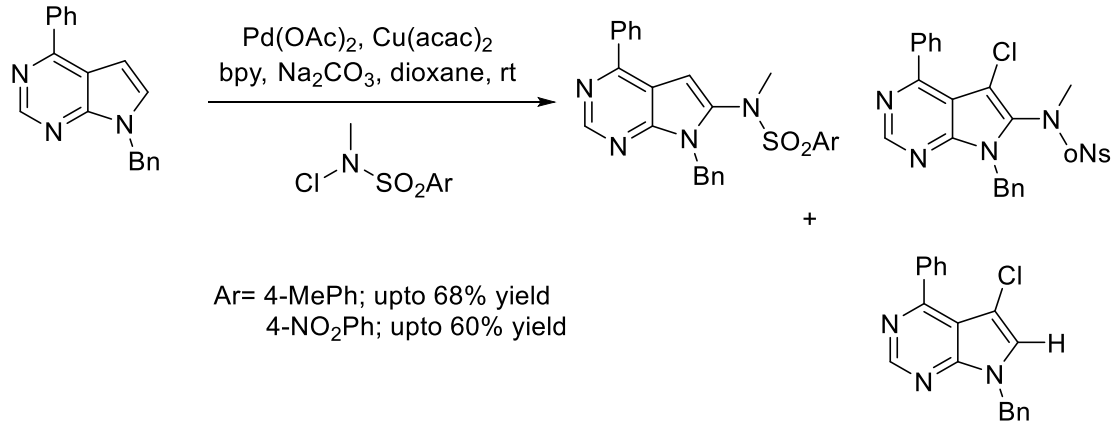


Figure 69. $Pd(OAc)_2/Cu(acac)_2$ promoted direct C–H amination and C–H chloroamination of 7-deazapurines

3.0. Multicomponent domino reactions for the synthesis of sulfonamides

Copper(I)bromide was used as an excellent catalytic material for synthesizing 2-(aminomethyl)indoles three-component domino cascade process involving reaction of 2-ethynylanilines with secondary amine and aldehyde. The reaction proceeded by the coupling−cyclization process using dioxane as a solvent. The reaction system performed via domino reaction involving C-3 functionalization of indoles effectively promoted the transformation of a cyclic or acyclic secondary amine and aldehyde (paraformaldehyde, aliphatic or aromatic aldehydes), 2-ethynylanilines into a broad range of 2-(aminomethyl)indoles. Mechanism for the three component domino cascade process involving three component coupling-cyclization of 2-ethynylanilines with secondary amine and aldehyde results in the formation of intermediates **1** and **2**. Thereafter, intermediates **1** and **2** react to form intermediate **3** followed by its rearrangenet to form final nitrogen heterocycle (Figure 70).**[115]**

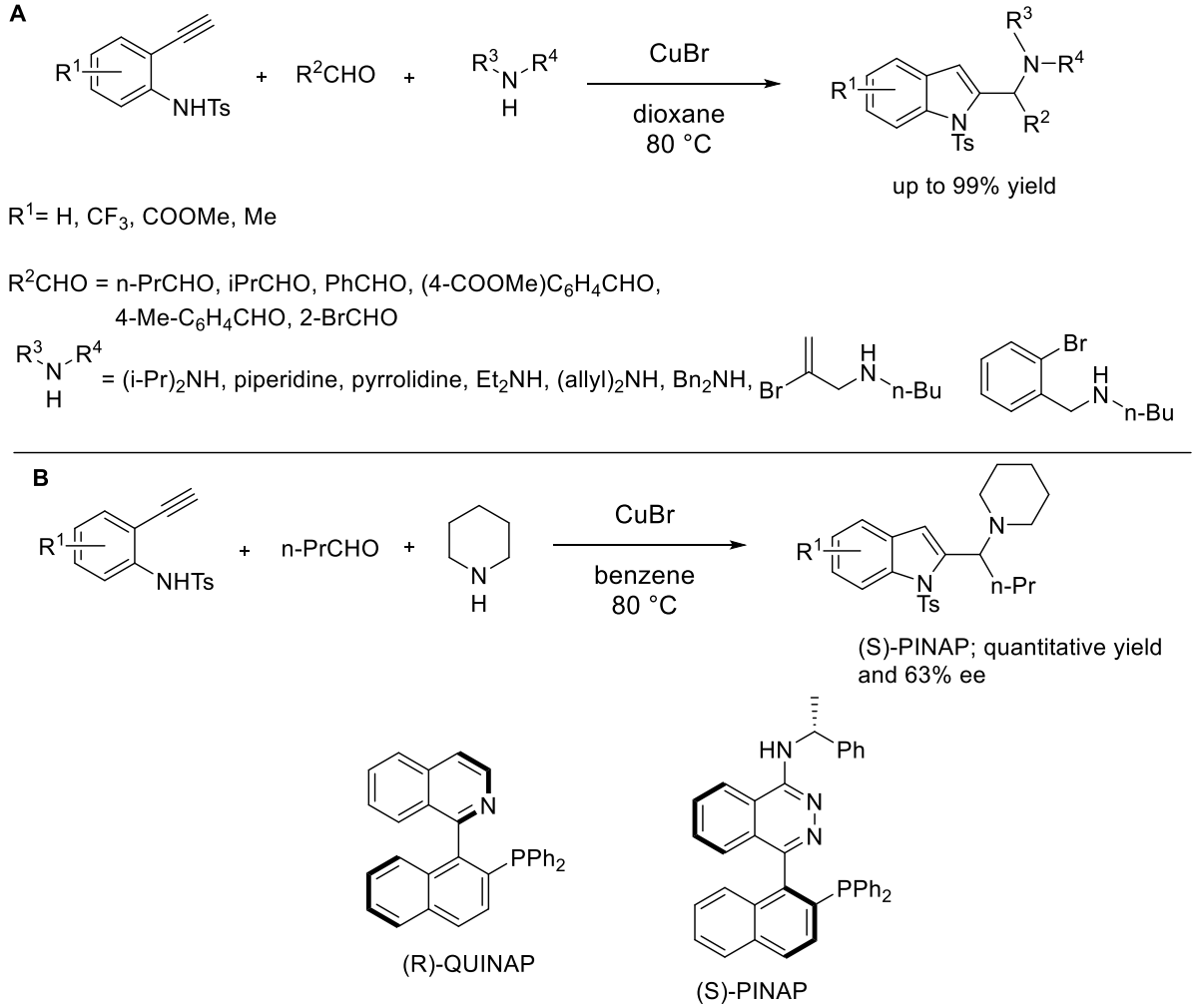
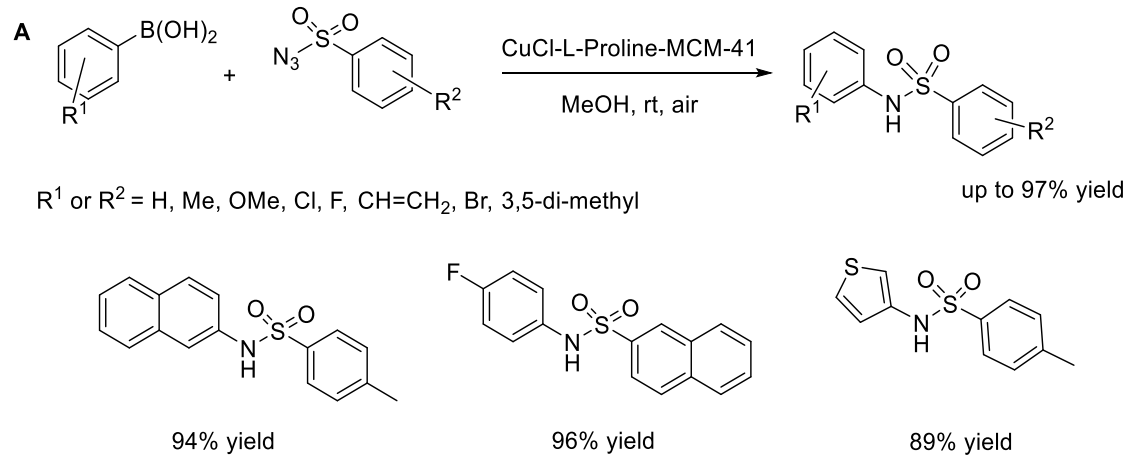


Figure 70. Copper(I)bromide effectively catalyzed synthesis of nitrogen heterocycles having aminomethyl group via multicomponent reaction

CuCl-L-proline-MCM-41 based heterogeneous recyclable enables Chan–Lam coupling between sulfonyl azides and arylboronic acids using methanol as solvent under ambient

conditionsusing 10 mol% of aforementioned catalyst. The catalytic reaction was performed under aerobic conditions, leading to a broad range of *N*-arylsulfonamides in excellent yields. The most plausible catalytic cycle for the oxidation of **1** with molecular oxygen results in the formation of intermediate **2**. In the next step, the intermediate **2** reacts with RSO_2N_3 to form intermediate **3** followed by reaction with arylboronic acid to form intermediate **5**. Furthermore, intermediate **5** is oxidized to form intermediate **6**. Finally, the intermediate **6** rearranges to final product **P** and regeneration of catalyst (Figure 71).[116]



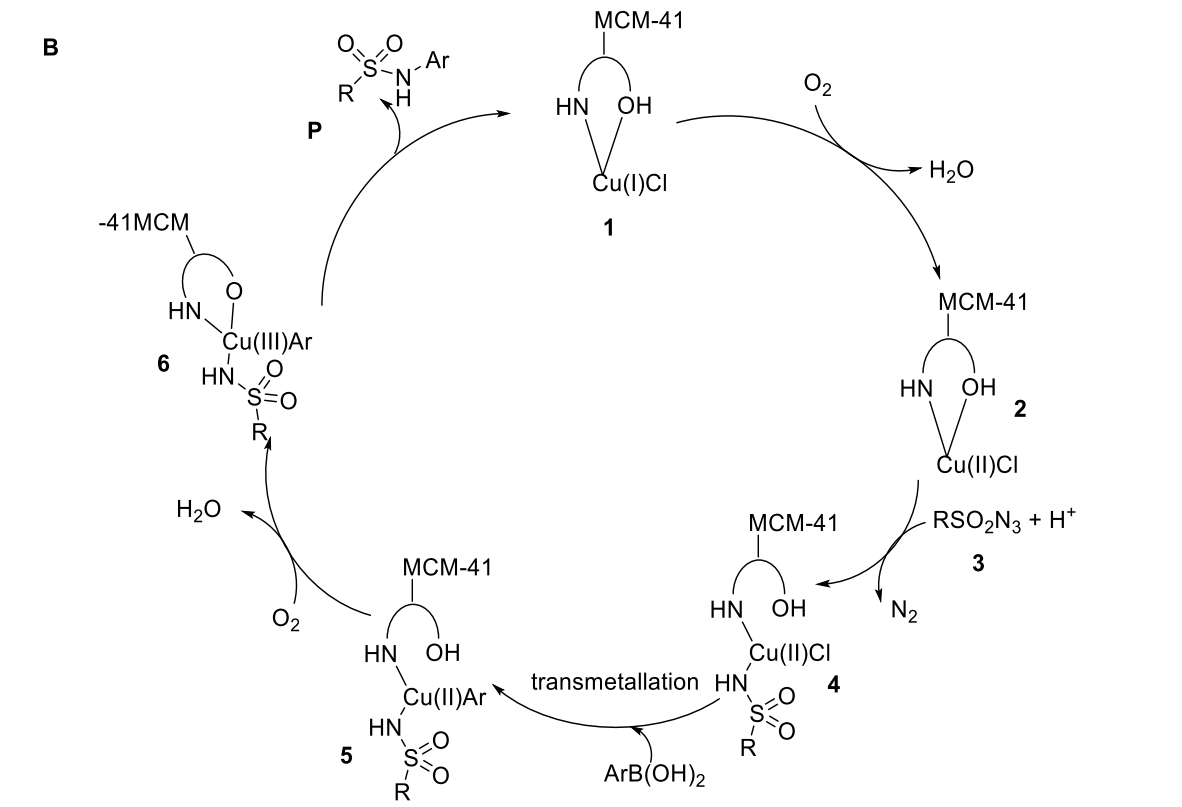


Figure 71. CuCl-L-proline-MCM-41 facilitated Chan–Lam coupling between sulfonyl azides and arylboronic acids to form *N*-arylsulfonamides

An impressive and new [3 + 3]-cycloaddition of α-diazocarbonyl compounds with *N*-tosylaziridines via synergetic catalysis of AgOTf and $Cu(OAc)_2$ has been well described, which offers efficient access to highly substituted 2*H*-1,4-oxazine derivatives. A variety of α-diazocarbonyl compounds and *N*-tosylaziridines were compatible substrates with convenient operations under mild reaction conditions. The mechanism for the reaction of α-diazocarbonyl compounds with *N*-tosylaziridines results in the formation of starts with activation of **1** with AgOTf and **2** with copper acetate [$Cu(OAc)_2$] to form intermediate **3** and **4** respectively. The intermediates **3** and **4** undergos [3+3] cycloaddition to form final product **5** (Figure 72).[117]

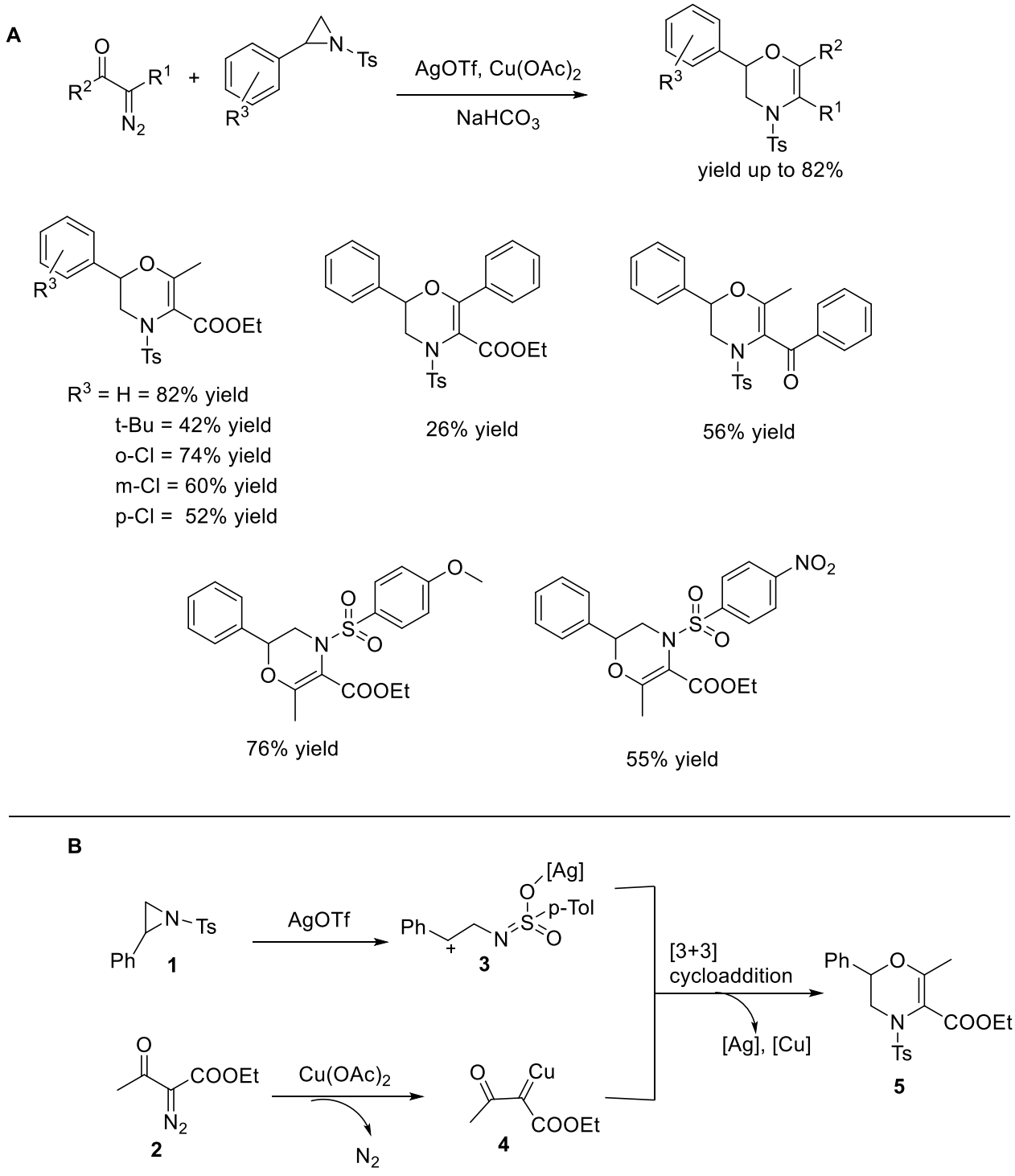


Figure 72. $Cu(OAc)_2$/AgOTf promoted synthesis ofpolysubstituted 2*H*-1,4-Oxazines [3 + 3]-by cycloaddition of α-Diazocarbonyl Compounds and *N*-tosylaziridines

Copper(I) based catalyst was used for the facile method to synthesize a variety of biologically significant compounds having DOTA-conjugated monomeric, dimeric, and tetrameric [Tyr^3]octreotide-based analogs assisting in the tumor imaging and radionuclide therapy. The aforementioned catalytic material was used to synthesizethio acid/sulfonyl azide amidation

by 1,3-dipolar cycloaddition of peptidic azides with dendrimer-derived alkynes (Figure 73).[118]

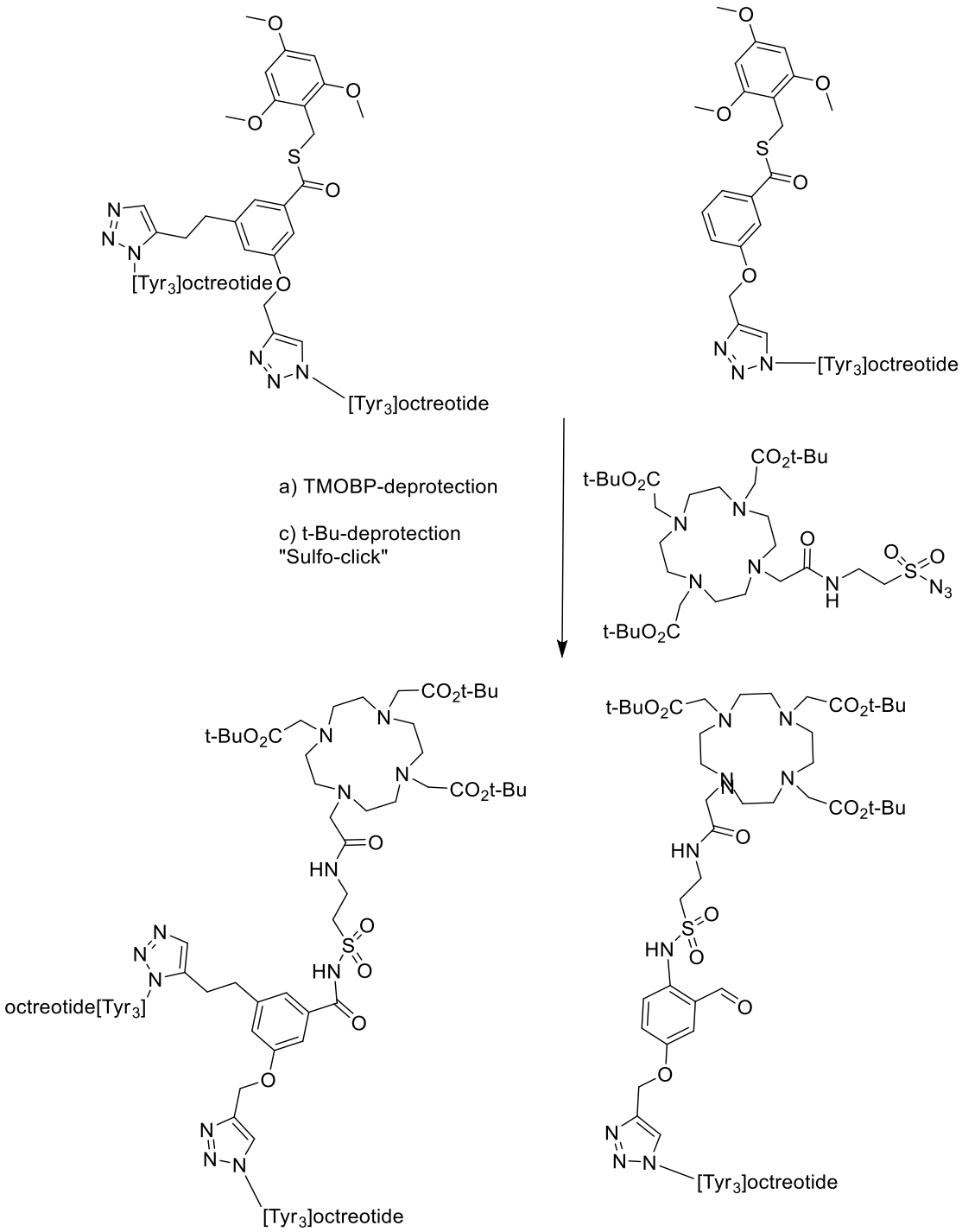


Figure 73. Copper-catalyzed synthesis of DOTA conjugated biologically active compounds

Copper iodide catalyzed N-arylsulfonamides synthesis by reacting the carboxylic acids with ynone and sulfonyl azide via CuAAC/ring-opening and Mumms type rearrangement. Mechanistic investigation shows that *N*-sulfonyl acetylketenimine was generated as a highly

reactive intermediate during the catalytic process. In the catalytic process, N-arylsulfonamides were formed in good to excellent yields (Figure 74).[119]

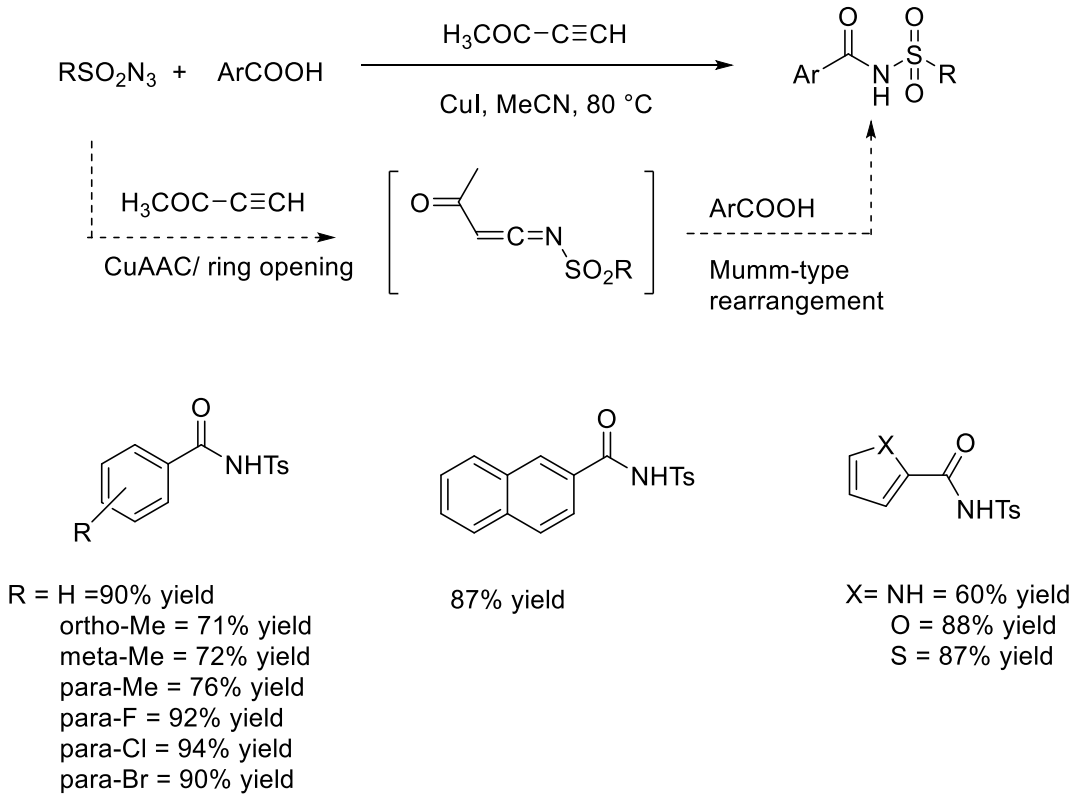


Figure 74. Synthesis of N-arylsulfonamide by reacting the carboxylic acid with sulfonyl azide and ynone using copper iodide catalyst

Aminonicotinamides are important scaffolds used for multifarious biological applications like antimicrobials, platelet derived growth factor receptors (PDGFR), hypoxya-inducible factors (HIF)-1α and intigrin $\alpha_v\beta_3$. [120] [121] [122] [123] Copper(I)chloride effectively promoted aminative aza-annulation of enynyl azide with *N*-fluorobenzenesulfonimide (NFSI) as an amination reagent under moderate reaction conditions and di-chloroethane as a solvent. The aforementioned cyclization process proceeds by regioselective inter-intramolecular diamination followed by incorporating nitrogen atom assisted by NFSI results into amino-substituted nicotinate derivatives. The one-pot process involving an efficient atom-economy reaction involving aminonicotinates by C–N bond-coupling (Figure 75).[124]

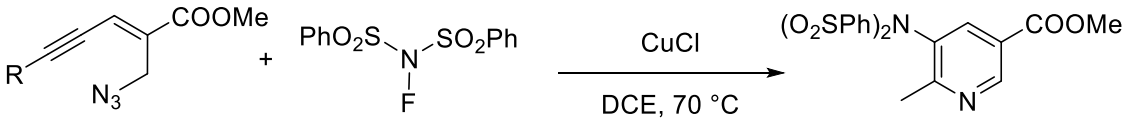


Figure 75. CuCl catalyzed synthesis of 5-aminonicotinates from enynyl azide and *N*-fluorobenzenesulfonimide

The catalytic pathway for the 5-aminonicotinates synthesis initiates with the NFSI mediated oxidation of Cu(I) to intermediate complex Cu(III)-N intermediate complex (**I**). The intermediate **I** transforms to the bis-sulfonylamidyl intermediate (**II**) by redox isomerization. The product (**II**) by intermolecular addition of alkyne to enynyl azide radical **C** to form intermediate **C**. The transformation of the intermedate (**III**) occurs by the two plausable pathways, that is, path **A** and path **B**. In the pathway **A** involves the transformation of the radical intermediate **III** with the Cu(II) interediate to form intermediate **V**. Interrmediate **V** by intraolecular reaction generates intermediate **VI** amd eliminates HF and N_2 (See Figure

76).

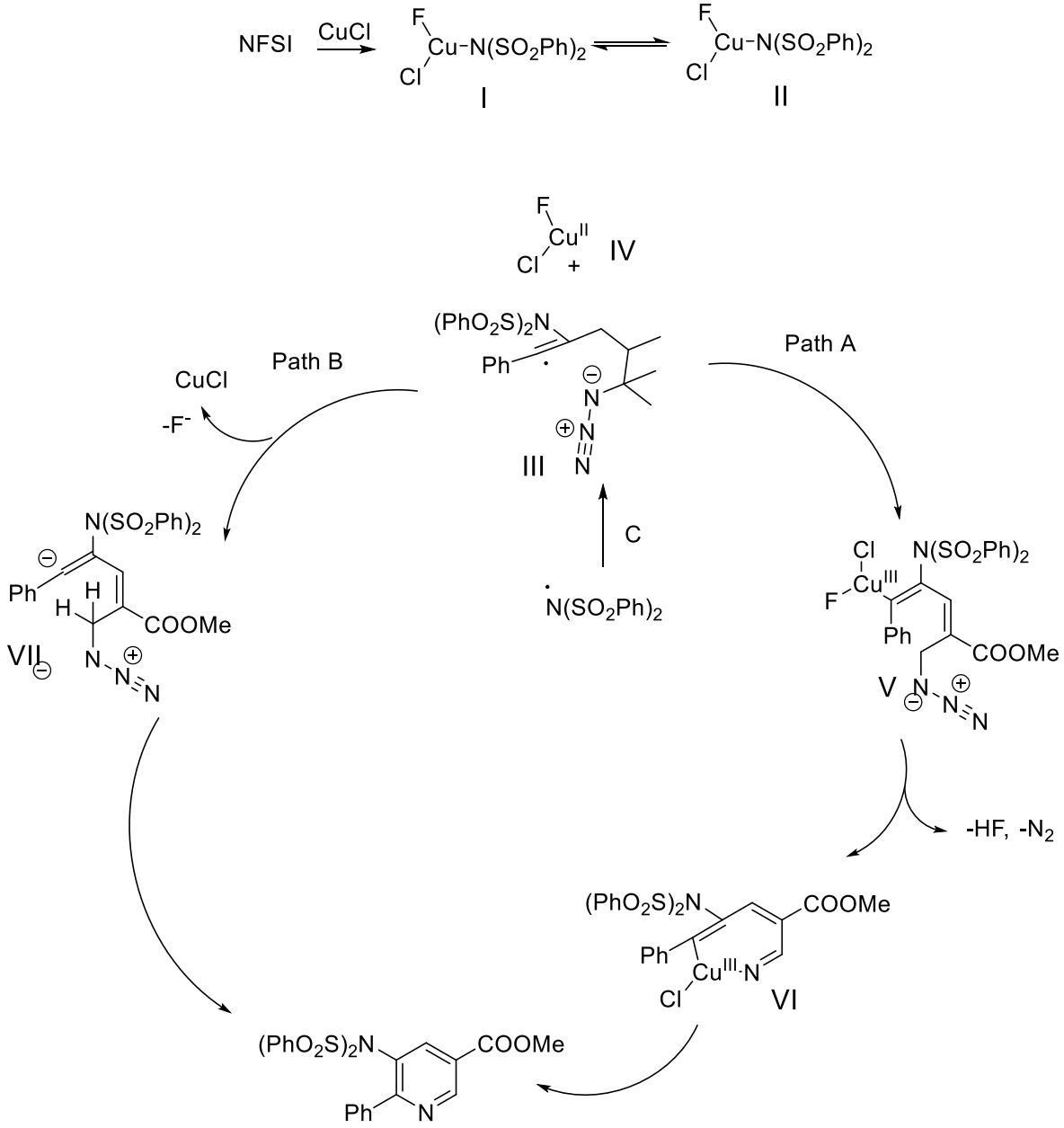
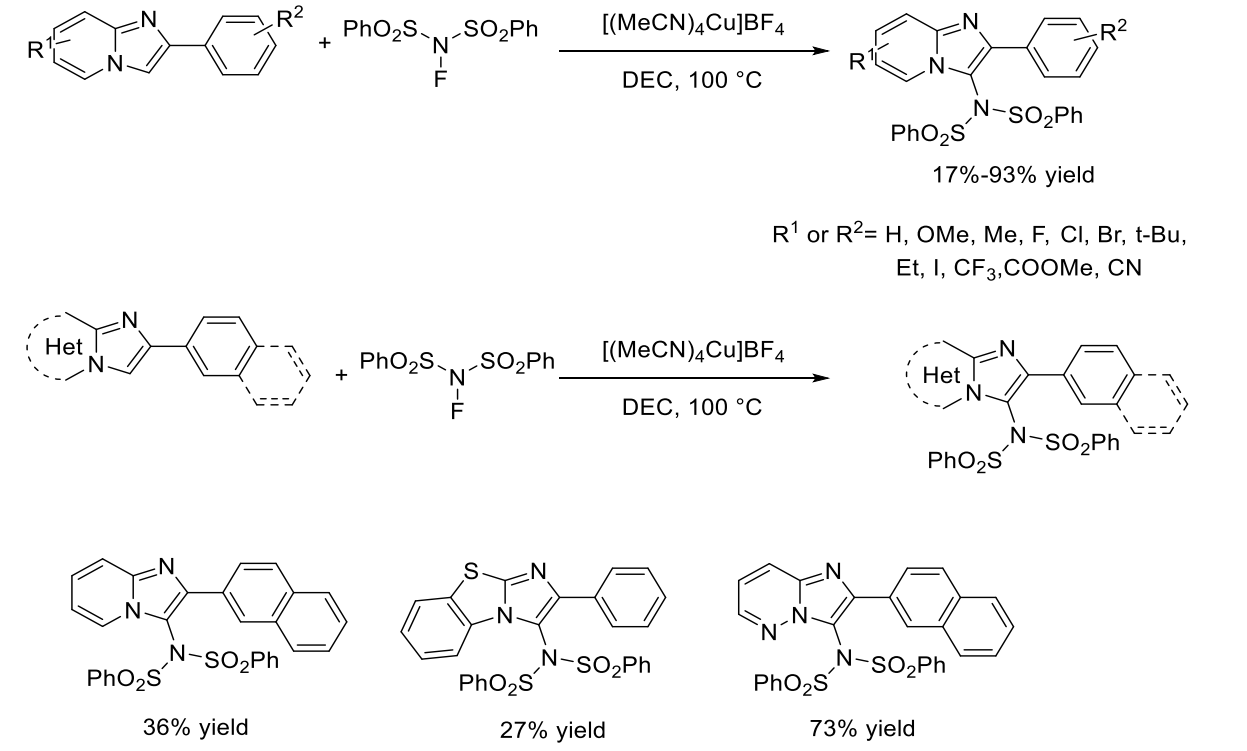


Figure 76. Mechanistic pathway for the copper catalysed synthesis of 5-aminonicotinante

In the final step intramolecular cyclization and removal of CuCl takes place liberating final product. According to the alternative pathway **B** the intermediate **III** could be oxidised to intermediate Cu(II) (**IV**) to form positively charged intermediate species **VII.** In the final step the intermediate species **VII** liberated nitrogen and HF to form the final heterocyclic product**.**

Nitrogen-containing heterocyclic compunds are are pivotal organic moieties that can be investigated as important biological moieties and valuable pharamcophores. Amongst all, imidazole pyridines composed of both imidazoles and pyridines possess antifungal agents, kinase inhibitors, H_1-receptors antagonists and antilipases. [125] [126] [127] [128] $[(MeCN)_4Cu]BF_4$

promotes the amination of C3 imidazopyridines for additive-free conditions at 100°C using dichloromethane as a solvent *N*-fluorobenzenesulfonimide (NFSI) as the amino source. The catalytic system promoted C3 animation with broad substrate scope and tolerating a variety of functional groups. The most plausible mechanim initiates with the reaction of NFSI (**1**) with Cu(I) catalyst (**1a**) to form radical intermediate **2** that exist in equiblirum with intermediate **3**. In the following steps, intermediate **3** reacts with **4** to form intermediate **5**, followed by the reaction of **5** with **1** to form intermediate **6**. Finally, intermediate **6** undergoes reformation to generate final product **7** (Figure 77).[129]



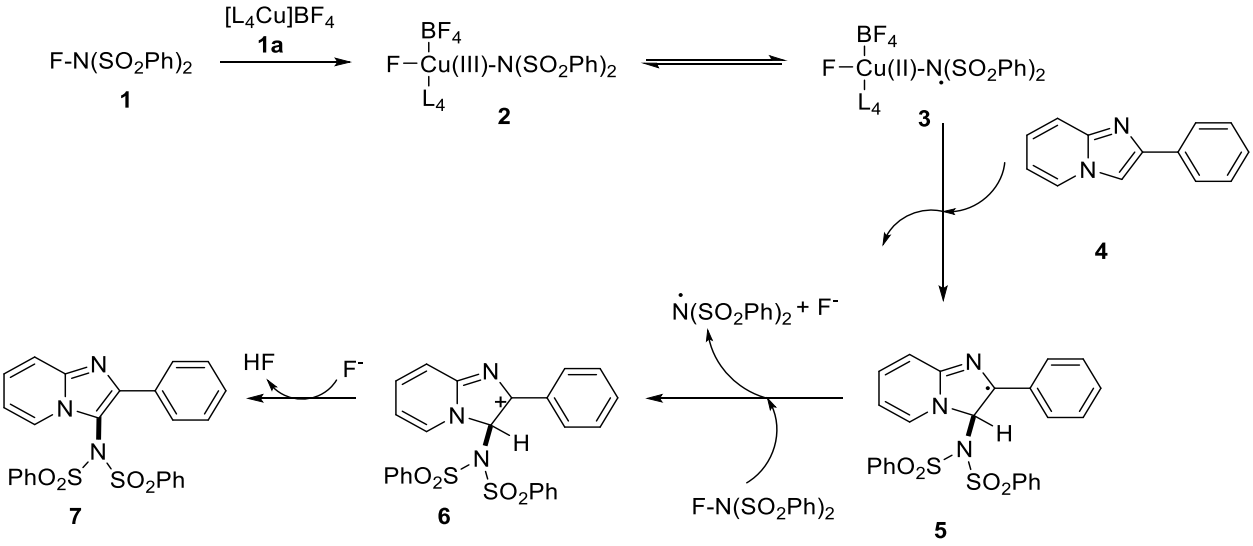


Figure 77. $[(MeCN)_4Cu]BF_4$ effectively promoted the amination of imidazopyridines with *N*-Fluorobenzenesulfonimide

Copper(II)triflate promotes multicomponent reaction without the assistance of any ligand involving alkynes, amines sulfonamides to form N-alkylated sulfonamides. The catalytic system promoted the reaction of a broad range of nitrogen sources with alkynes and multifarious aldehydes(silyl, aryl, alkyl, halogenated, and heteroaryl groups). The reaction

system effectively promoted alkynylation involving *p*-toluenesulfonamide assisting in providing high yields for*N*-Ts-protected propargylamines (Figure 78).[130]

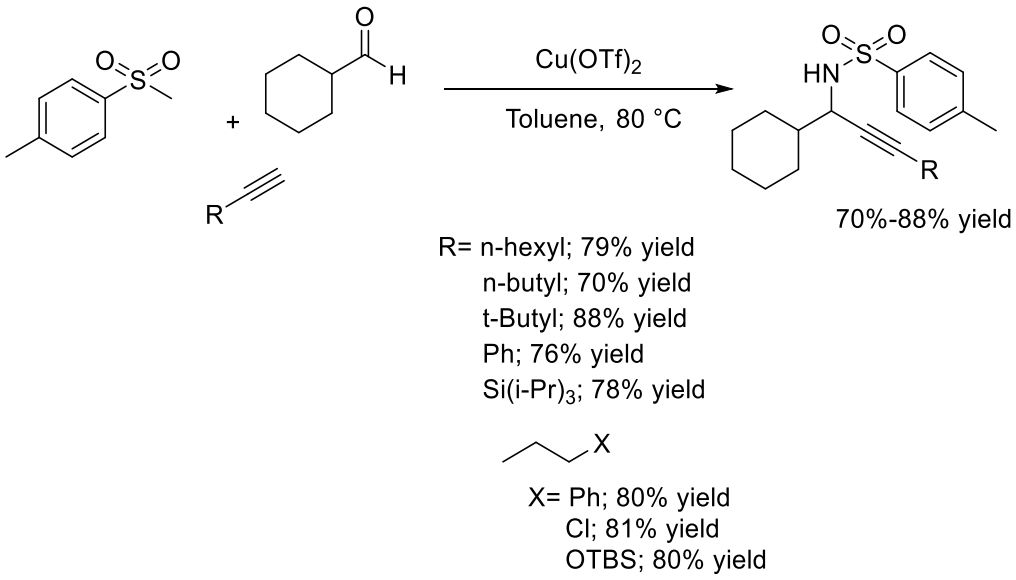
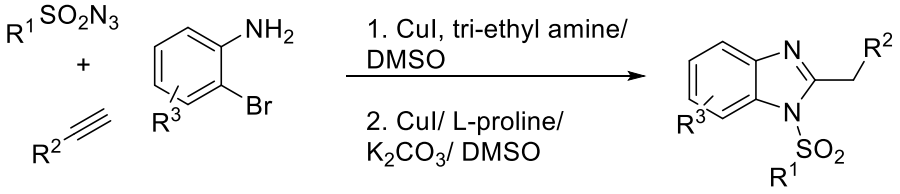


Figure 78. Copper(II)triflate catalyzeda three-component reaction for the synthesis of N-alkylated sulfonamides

2-substrituted benzamidazoles are significant pharmacophores occuring in drugs and bioactive compounds.[131] [132] Copper(I)iodide/triethylamine (TEA) catalyzed multicomponent reaction involving functionalization of benzimidazoles by reacting sulfonyl azides, alkynes and 2-bromoaniline. The reaction was performed in DMSO as a solvent using tri-ethylamin or K_2CO_3 as a base through the mechanism involving intramolecular products in moderate to good yields for 2-substituted -sulfonylbenzamidazole. (Figure 79) [133]

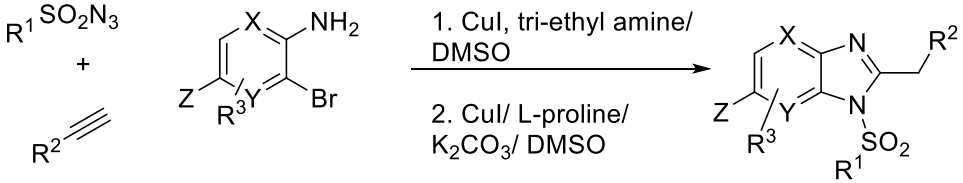


up tp 78% yield

R^1= 4-MeC_6H_4, C_6H_5, 4 ClC_6H_4, 4-i-PrC_6H_4, 4-MeOC_6H_4, n-Bu, Me

R^2= Ph, 4-MeC_6H_4, 3-MeC_6H_4, 3-FC_6H_4, n-Bu, n-prntyl, TMS

R^3= H/Br, 4-Me/Br, 4-Cl/Br, H/I, H/Cl



X= CH, N; Y= N, CH; Z= H, Me

Imidazopyidines

Figure 79. Copper(I) iodide promoted multicomponent synthesis of benzimidazoles from sulfonyl azides, alkynes and 2-bromoaniline

The multicompornet reaction for the sufonylbenzimidazole derviatives synthesis initiates by the interaction of copper(I) iodide, TEA, sulfonyl azide reaction with alkyne to ketenimine species **A**. The ketenimine intermediate rapidly reacts with the nucleophile **3** generating sulfonylamidine **B**. The resulting intermediate **B** tautomerizes to form **C**. In the final step, copper(I) iodide, L-proline and K_2CO_3 promote intramolecular C-N coupling of sulfonamides by interconvertable to form the desried sulfonylbezimidazole dervatives (See Figure 80).

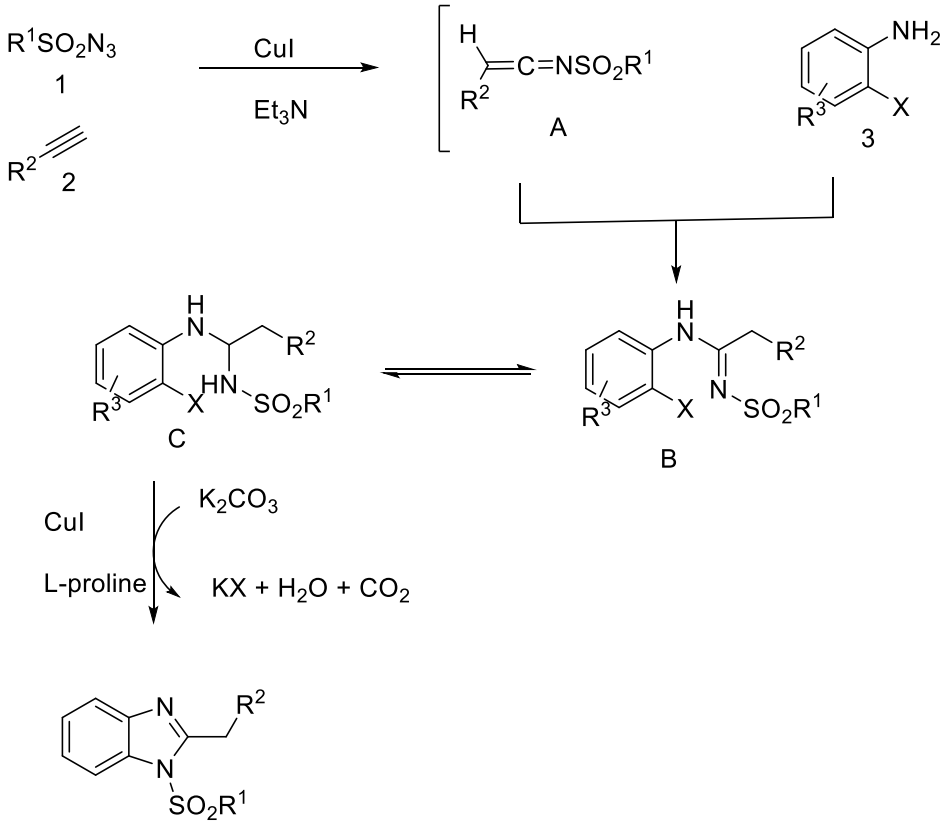


Figure 80. Plausable mechanism for the copper catalysed benzimidazole synthesis

Copper(I) thiophene-2-carboxylate (CuTC)/DMEDA/Cs_2CO_3 enables the synthesis of allylic allenic amides by cross-coupling between allylic sulfonamides and bromoallenes. The desired allylic allenic amides were obtained in moderate to excellent yields. The mechanism for the aformentioned reaction intiates with reaction of catalyst **1** with bromoallene **2** to form intermediate **3**. Thereafter, intermediate **3** reacts with **4** results in the formation of intermediate **5** that exists in equiblibrium with **6**. The intemediate **5** undeoges refomation to form final product **7** and regeration of catalyst (Figure 81).[134]

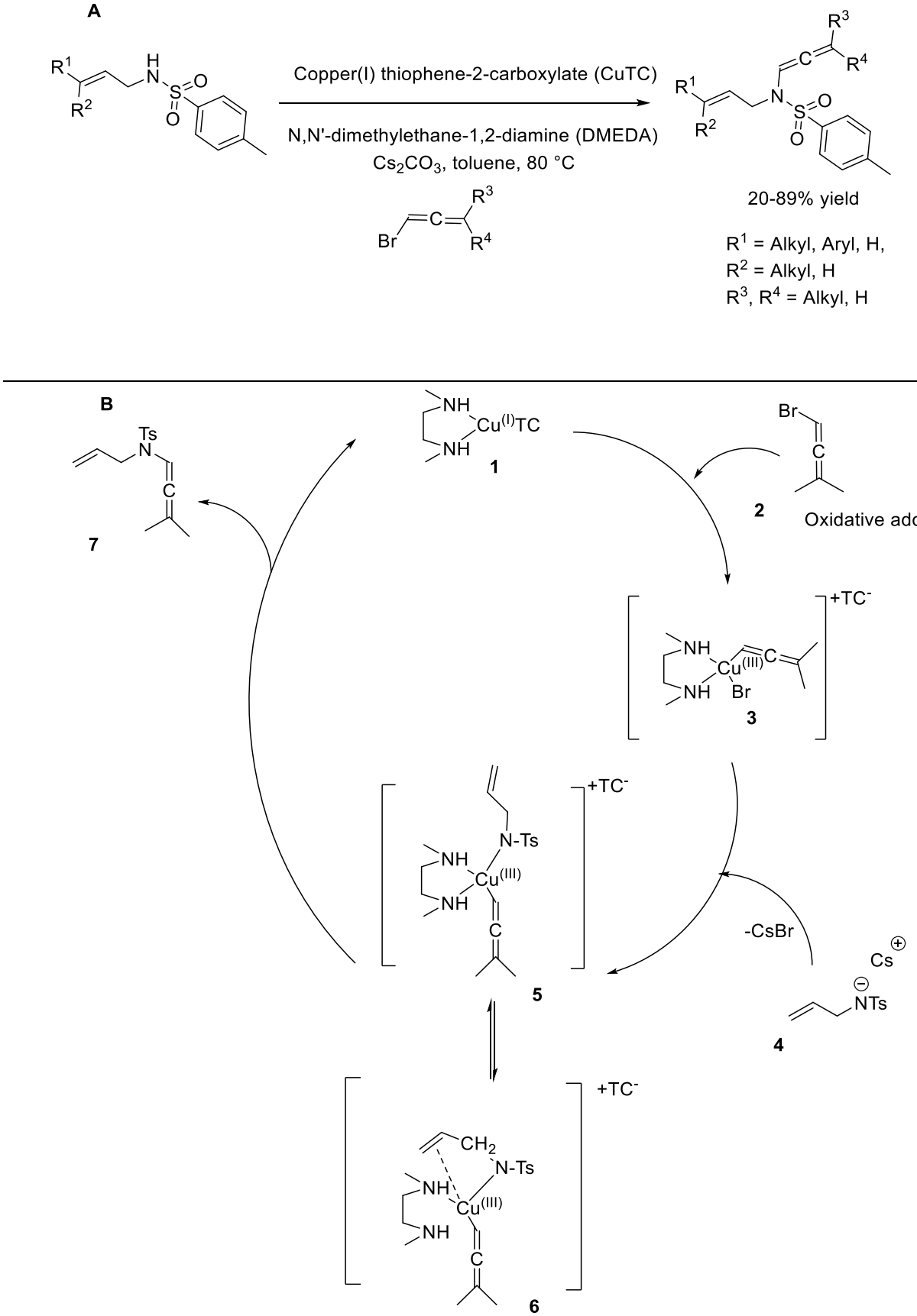


Figure 81. CuTC/DMEDA/Cs_2CO_3 promoted *N*-allenylation of allylic sulfonamides

Multicomponent reactioninvolving coupling between 1-alkynes, sulfonyl azides, and pyrrole derivatives to form 2-functionalized pyrrole rings was catalyzed by CuCl/Et_3N. The reaction involving carbon-carbon bond formation afforded excellent yields under moderate reaction conditions with broad substrate scope (Figure 82).[135]

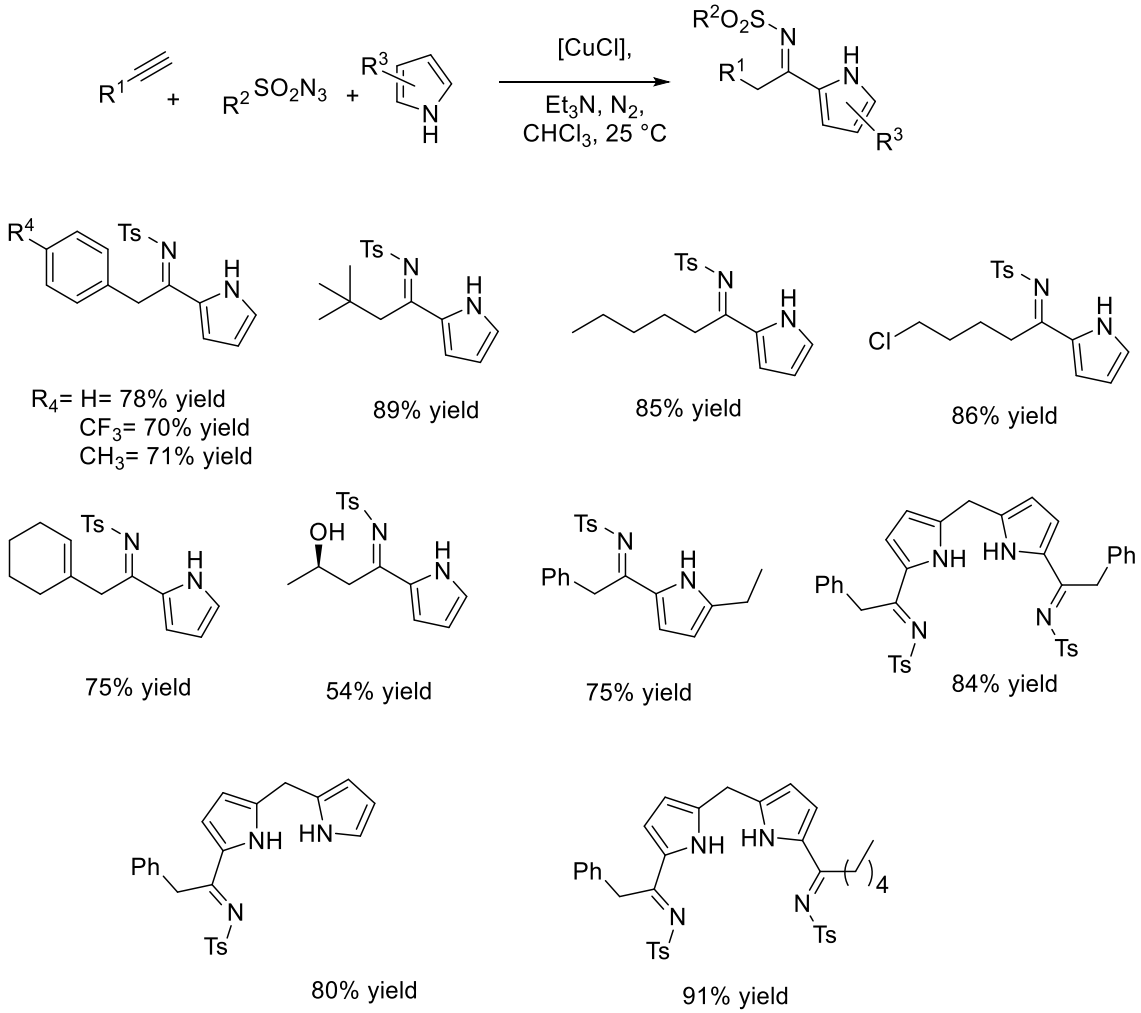


Figure 82. CuCl/Et_3N catalyzes multicomponent reaction involving synthesis of functionalization pyrrole rings

Keteimines are valuable intermedates for the synthesis of valuable heterocycles of different ring size via nucleophilic addition reaction. Copper(I)iodide/triethylamine promoted a one-pot tandem cascade intramolecular process involving the attack of nucleophilic at *N*-sulfonylketenimine, leading to the rearrangement of sulfonimidates to sulfonamides affording to synthesis substituted 8,9-dihydro-5*H*-imidazo[1,2-*a*][1,4]diazepin-7(6*H*)-ones (Figure 83).[136]

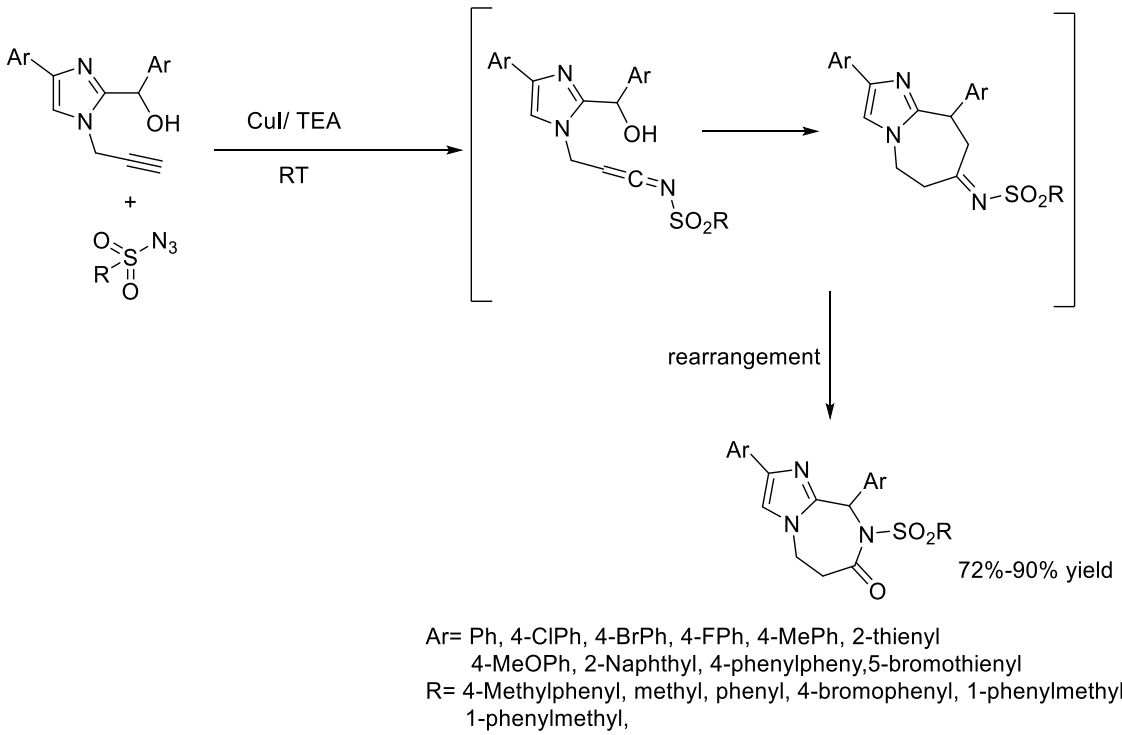


Figure 83. Copper(I)iodide/triethyl amine promoted cascade process to generate imidazo[1,2-*a*][1,4]diazepin-7(6*H*)-one

Sulfonyl amides are valuable synthetic intermediates for diversity of pharmaceutical compounds and drug discovery. [137] [138] [139] A three-component reaction of triethoxysilanes, sulfur dioxide, and hydrazines catalyzed by copper(II) acetate is reported, leading to *N*-aminosulfonamides in good yields. Not only triethoxy(aryl)silanes and triethoxy(alkyl)silanes are compatible during the insertion of sulfur dioxide. Additionally, diethoxy diaryl silanes are suitable under the conditions as well (Figure 84).[139]

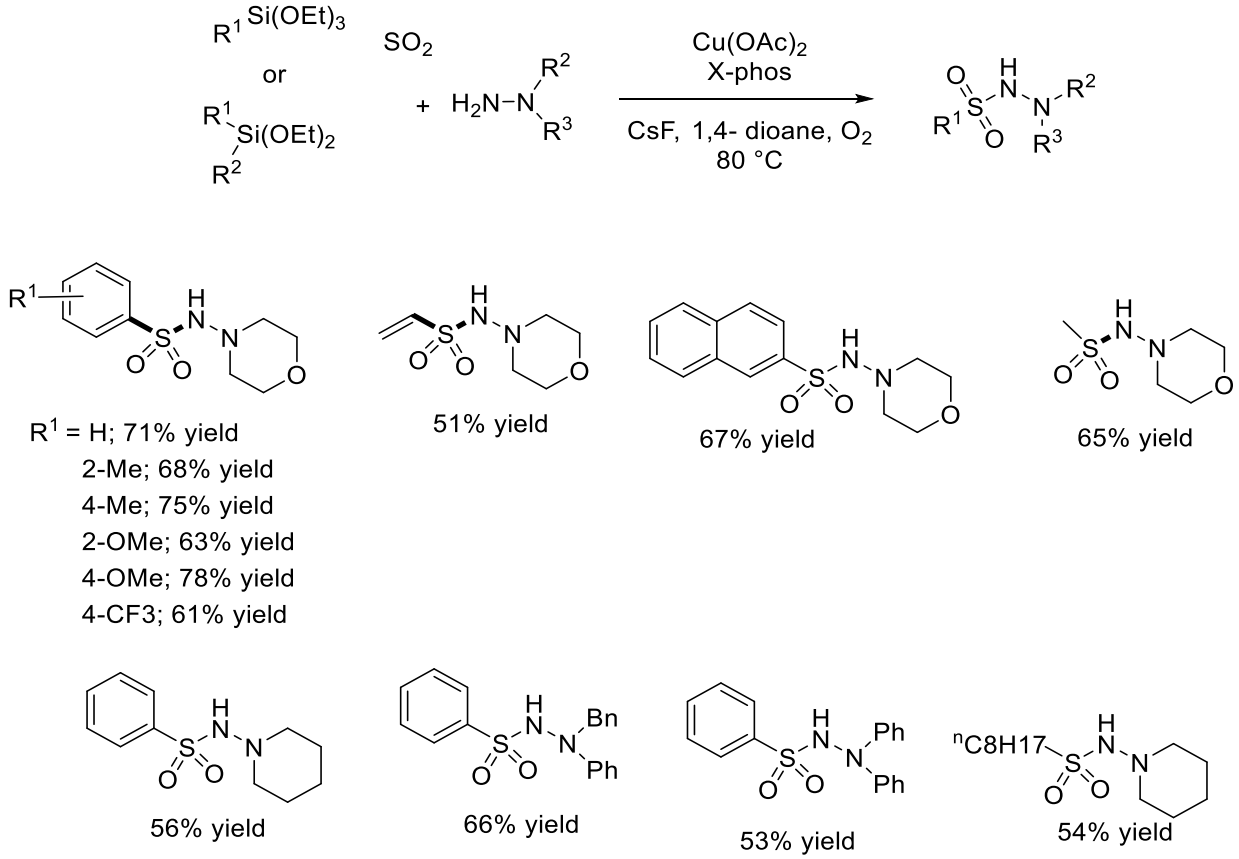


Figure 84. A Copper-Catalyzed Three-Component Reaction of Triethoxysilanes, Sulfur Dioxide, and Hydrazines

Copper(I)-thiophene-2-carboxylate (CuTc) effective catalyst for the C–H amidation process where azides were used as the amino surrogates under aerobic conditions. The aforementioned reaction was performed using dichlorobenzene (DCB) and pivalic acid (PivOH) as a solvent at 110 °C using argon (Ar) environment. The mechanistic studies reveal the reaction proceeded by the tandem process involving C–N/N–N bond formation resulting in the one-pot indazole derivatives formation (Figure 85). [140]

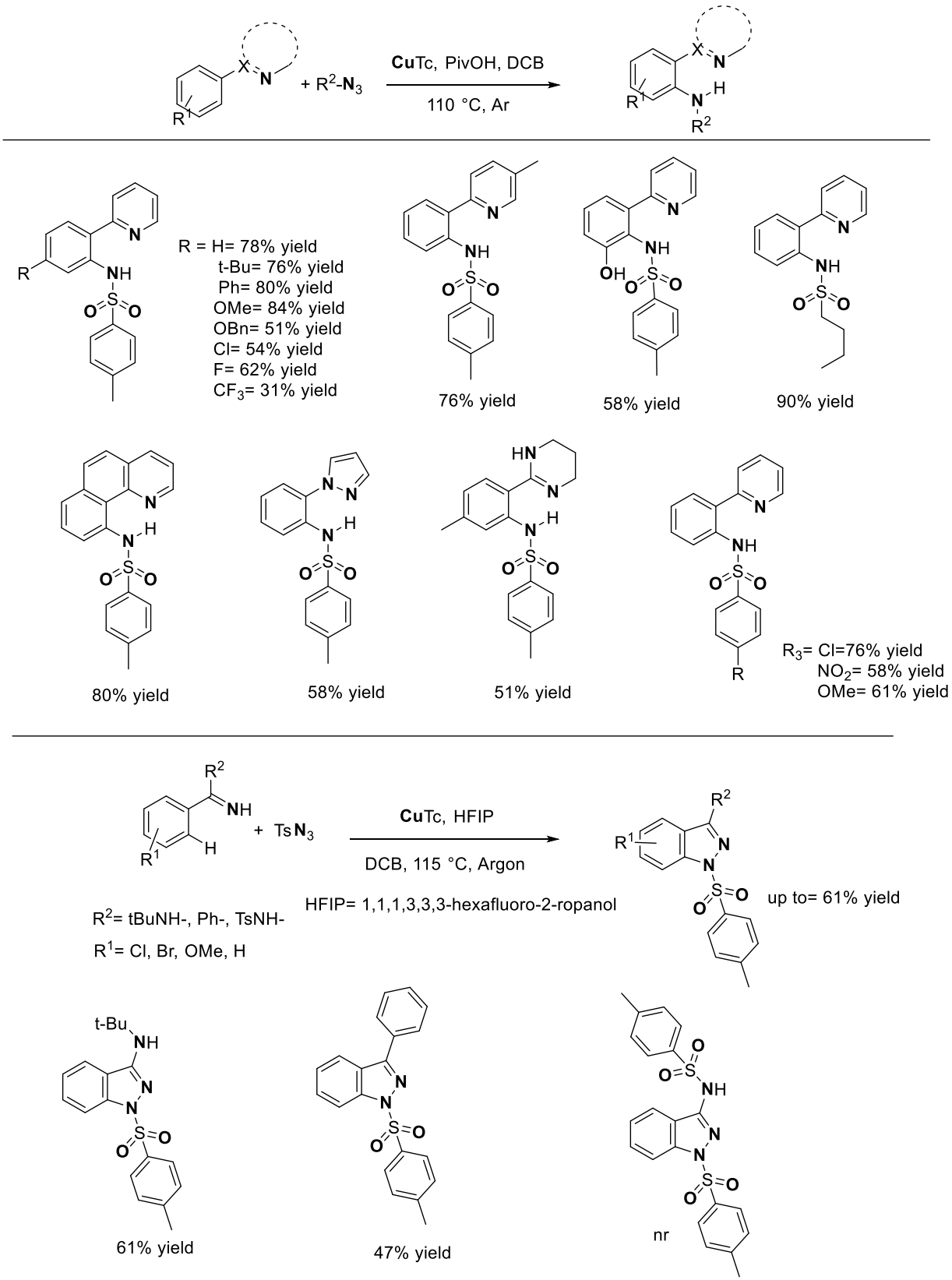


Figure 85. CuTc was used as the catalyst for the amidation with azides as amino sources

Wang et al investigated three component reaction involving nitroarenes, arylbrornic acid and potassium metabisulfite ($K_2S_2O_5$). The three-component reaction was promoted by copper

catalyst [Cu(NeCN)$_4$PF$_6$] and 1,10-phenanthroline (ligand). Moreover, IPA was used as the economical and easily separable reducing agent. A wide array of nitroarene and aryl boronic acids were transformed to N-substituted sulfonamides in moderate to good yields. Additional feature of the catalytic system was tolerance to different functional groups like cyano, amino, carbonyl and hydroxyl groups. Modification of commercially available drug flutamide was also performed using the aforementioned catalyst/ligand system (Figure 86).[141]

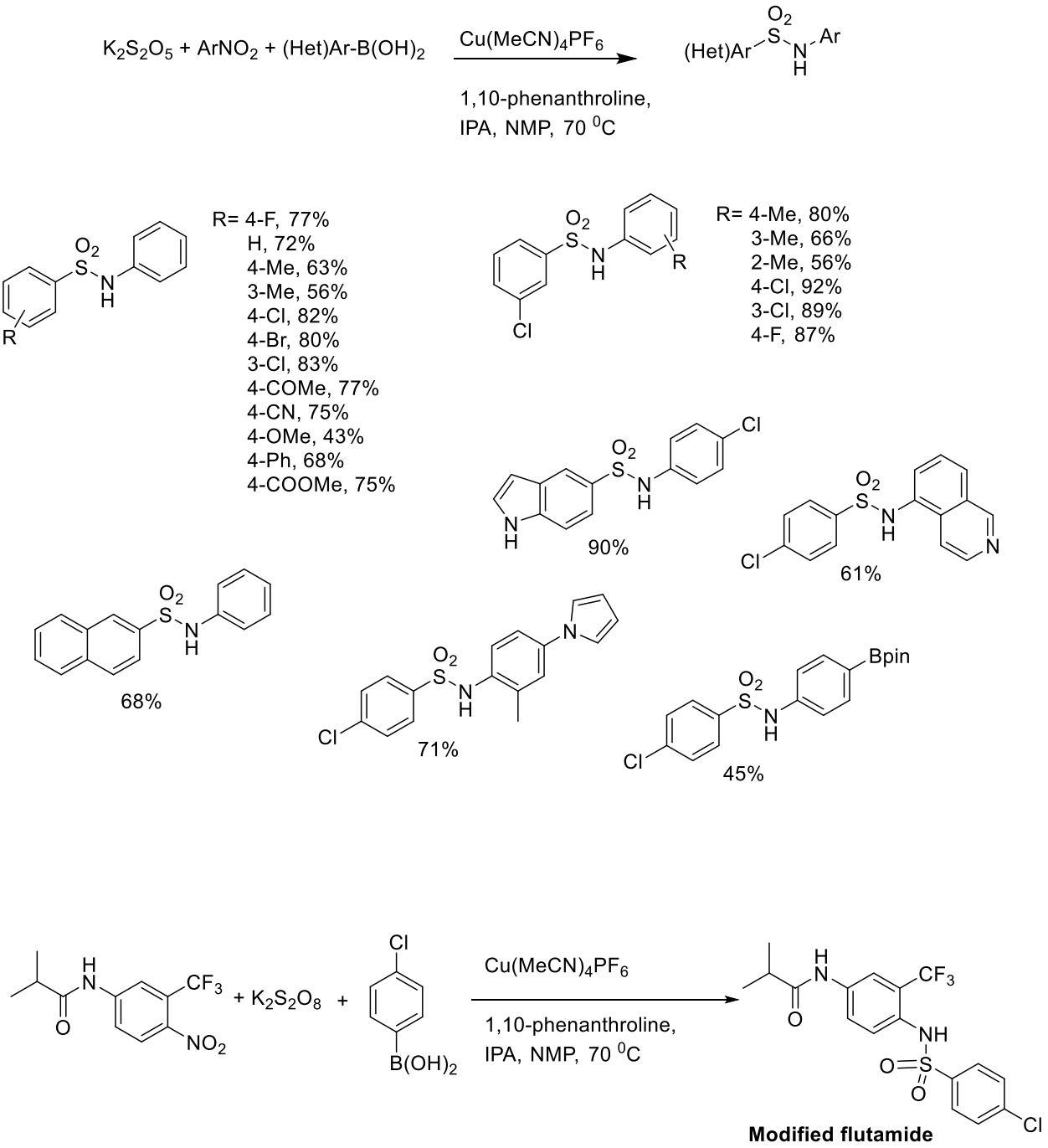


Figure 86. $[Cu(NeCN)_4PF_6]$/ 1,10-phenanthroline promoted synthesis of N-substituted sulfonamides

Plausible mechanism for the synthesis of synthesis of $[Cu(NeCN)_4PF_6]$/ 1,10-phenanthroline mediated N-arylated sulfonamides starts with activation of arylboronic acid **R2** and $K_2S_2O_5$ via intermediates A-B-C-D. The nitroaromatic compound **R2** interacts with copper catalyst to form intermediate **E**. The intermediate **E** and **D** interact with each other to form intermediate **F**. The intermediate rearranges via release of proton to form intermediate **G**. In the subsequent steps isopropanol assist reduction of intermediate **G** and **H** to form final product **P** (Figure 87).

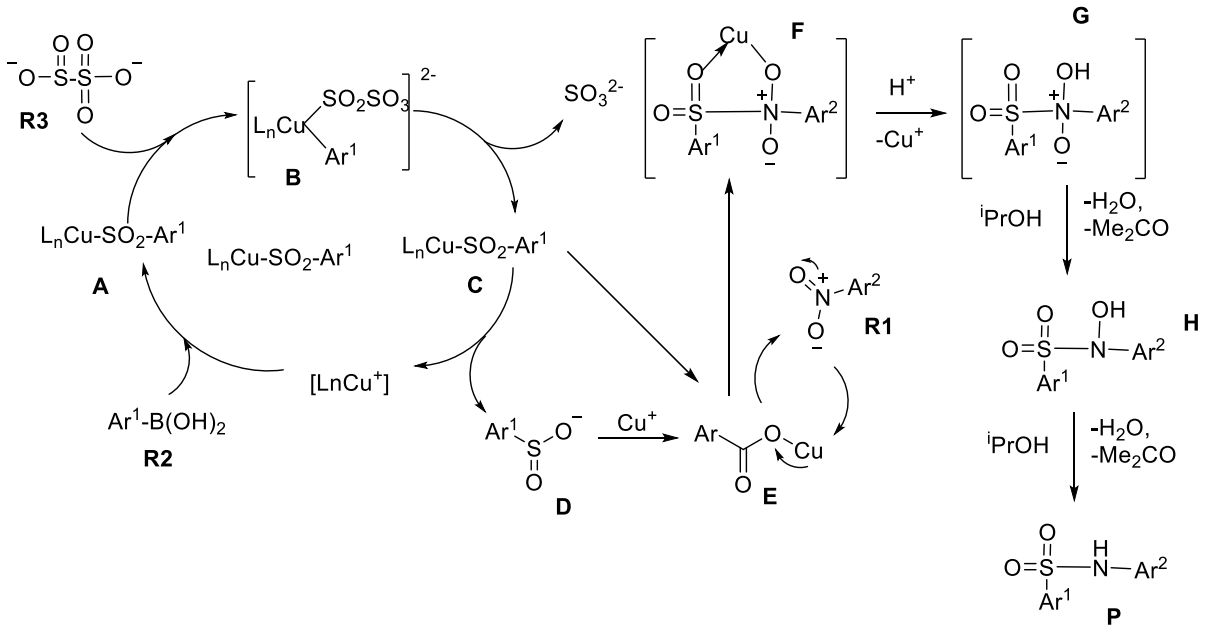


Figure 87. Mechanistic studies for the synthesis of N-substituted sulfonamides via multicomponent reaction involving nitroaromatic, arylboronic acid and $K_2S_2O_5$.

Liu and coworkers demonstrated trifluoromethylated sulfonamides syntheses using copper(II) triflate catalyst and $(bpy)Zn(CF_3)_2$ as the trifluoromethylation reagent. The reaction performed using $PhCF_3$/DCM solvent system and sodium acetate as additive at 70 °C. The reaction proceeds by the radical mediated 1,5-hydrogen atom transfer (HAT) reaction. The role of NaOAc is ambiguous, most probable role of sodium acetate was to accelerate the CF_3 transformation from zinc to copper. The progress of the reaction was hampered by stoichiometric amount of TEMPO or butylated hydroxytoluene (BHT). The mechanistic confirm that reaction follows by the disproportionation of Cu(II) to Cu(I) and formation of Cu(I)-CF_3 intermediate. The intermediate Cu(I)-CF_3 promotes the formation of N-radical

intermediate via single electron transfer. In the subsequent step, 1,5-hydroden atom transfer occurs (1,5-HAT) and generation of carbon radical. In the final step carbon radical reacts with CF_3 group to form C-CF_3 bond (Figure 88 and 89).[142]

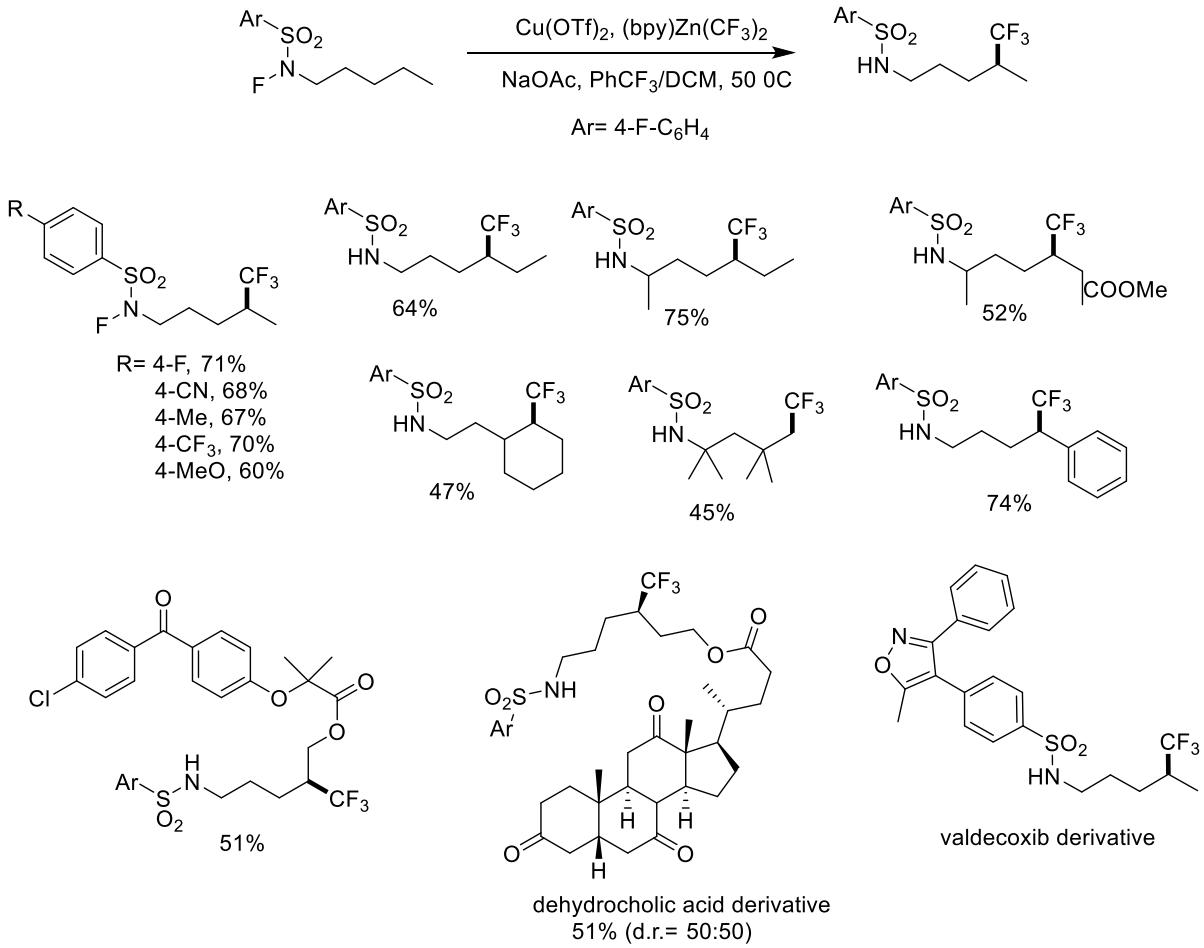


Figure 88. Copper(II) triflate catalyst and (bpy)$Zn(CF_3)_2$ promoted 1,5-HAT reaction

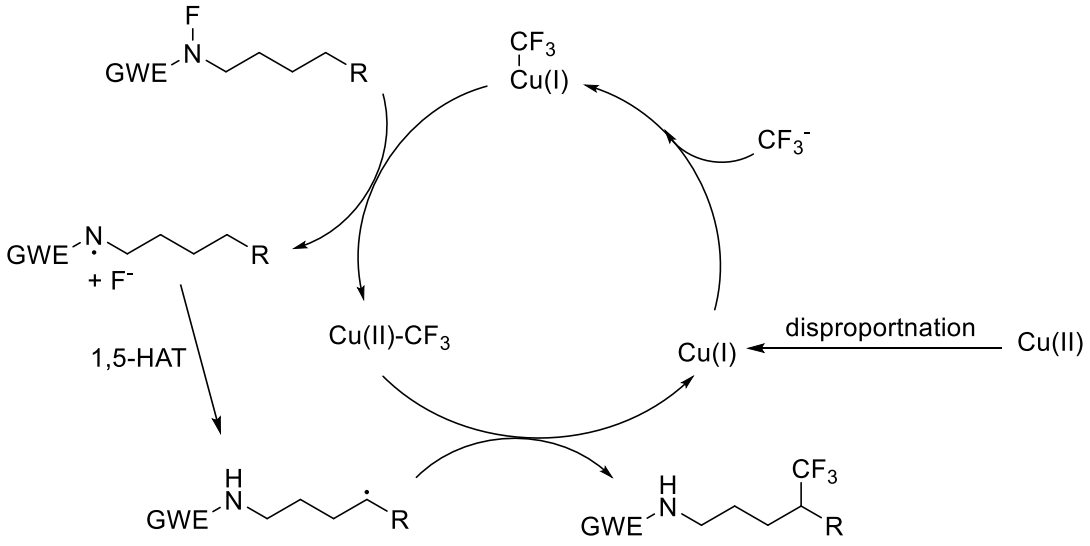


Figure 89. Mechanism for the copper (II) triflate catalyst and (bpy)Zn(CF_3)$_2$ promoted 1,5-HAT reaction

Cu($CF_3COCHCOCH_3$)$_2$/Fe(OTf)$_2$ in the presence of sodium-tert-butoxide promotes one-pot multicomponent reaction for the synthesis of C(sp^3)-H bond phosporothiolation of sulfonamides. The reaction was performed in the presence of S_8 and 4,7-diphenyl-1,10-phenanthroline (ligand) to form alkyl phosphorothioates having C(sp^3)-SP(O)(OR)$_2$. These phosphorothioate based functional groups are bioactive compounds are useful agrochemicals and medicinal compounds like amifostine, bensulide, vamidothion, etc. Additionally, these compounds are useful intermediates in organic synthesis. Mechanistic studies demonstrate sequential step involving generation of amidyl radical in the presence of Cu(I) [Cu(I) was generated by the reduction of Cu(II) in the presence of Fe(II). The resulting amidyl radical by 1,5-HAT assist in the formation carbon radicals. Finally, copper catalysed cross-coupling of the carbon radical reacts with in-situ generated (RO)$_2$P(O)SH radical to form phosporothiolationed sulfonamides (See Figure 90 and 91). [143]

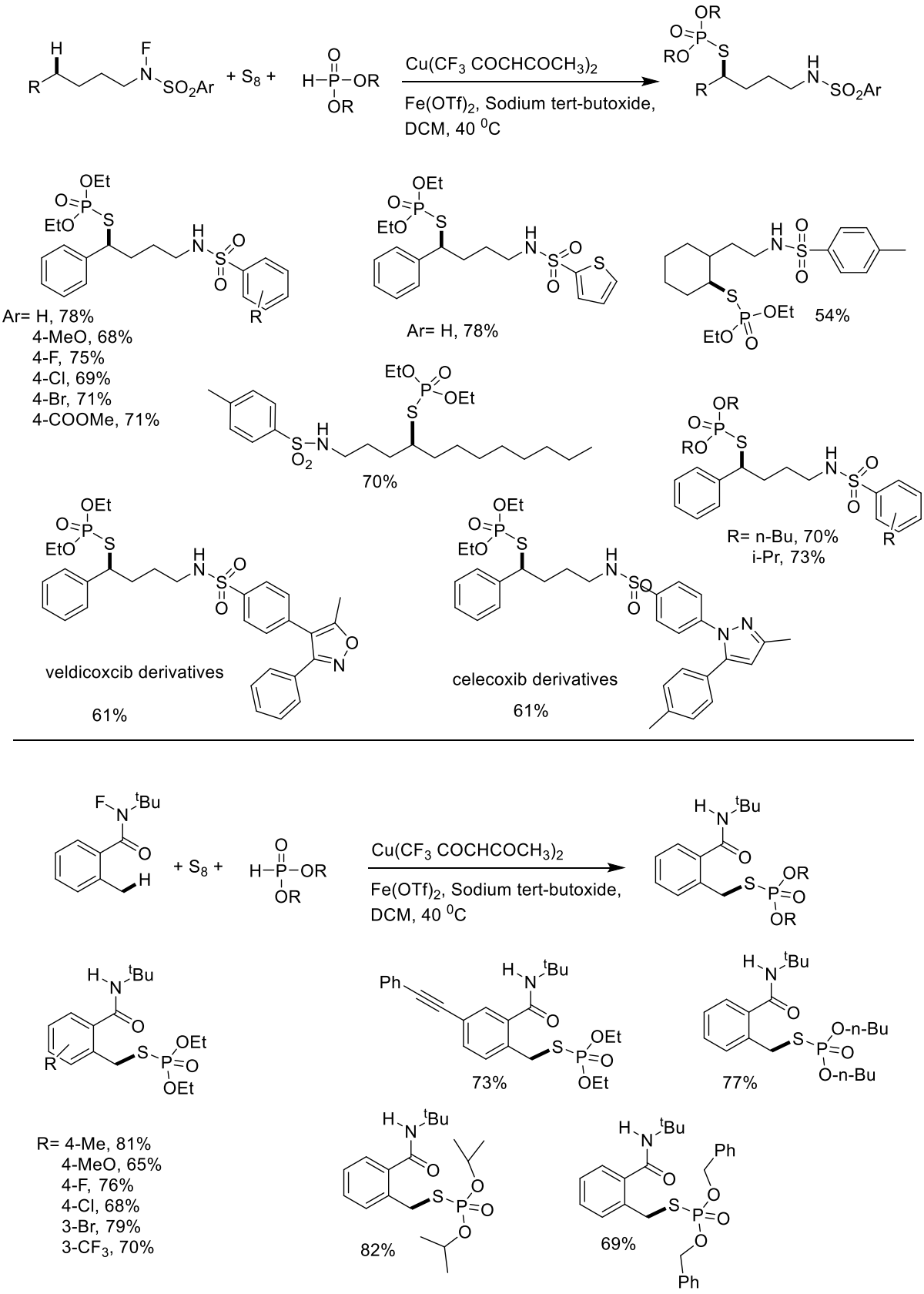


Figure 98. $Cu(CF_3COCHCOCH_3)_2/Fe(OTf)_2$ promoted $C(sp^3)$-H bond phosporothiolation of sulfonamides.

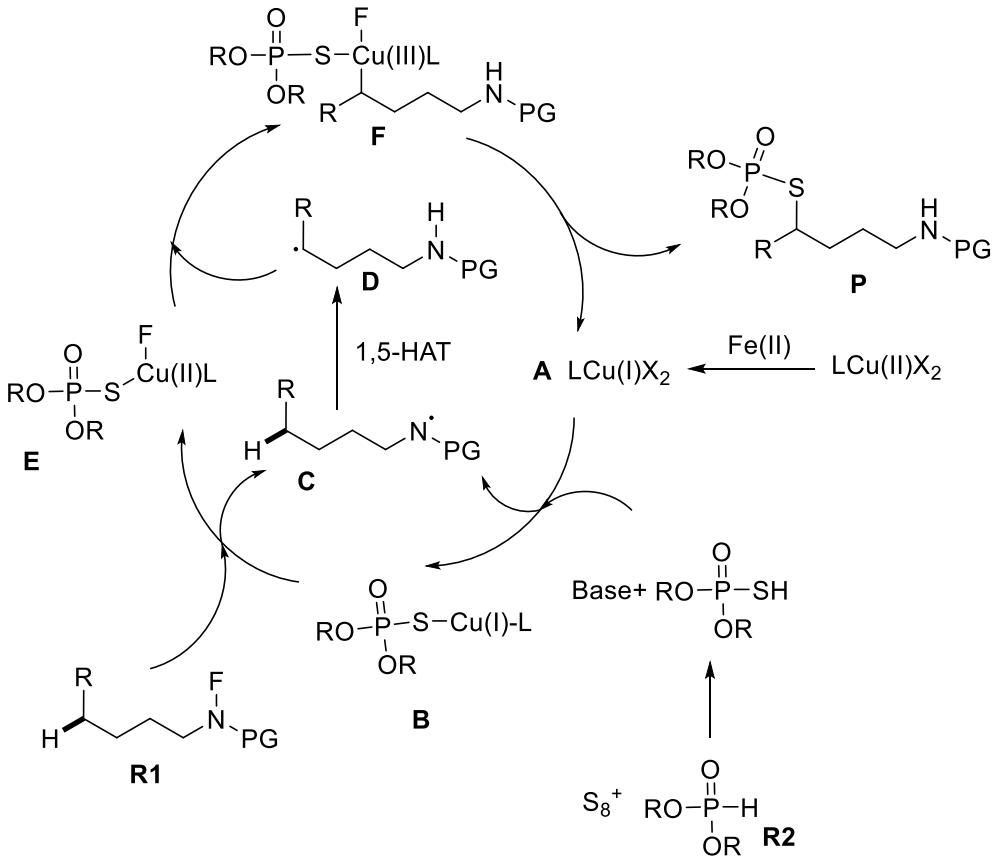


Figure 91. Mechanistic studies for the copper catalysed phosporothiolation of sulfonamides.

$Cu(OTf)_2$ in the presence of Li_2CO_3 base and 5,5'-dimethyl-2,2'-bypyridine ligand promote synthesis of N-sulfonyl-β-homoproline esters from N-fluoro-sulfonamides and alcohol at 100 °C and $PhCF_3$ and THF as solvent. The catalytic system promotes synthesis of diversity of β-homoproline esters in moderate to good yield. The β-homoproline derivatives are important intermediates find occurrence in biology and medicine. Mechanistic studies demonstrates that the reaction proceeds by the radical mechanism involving intramolecular cyclization and intermolecular carbonylation reaction (See Figure 92 and 93).[144]

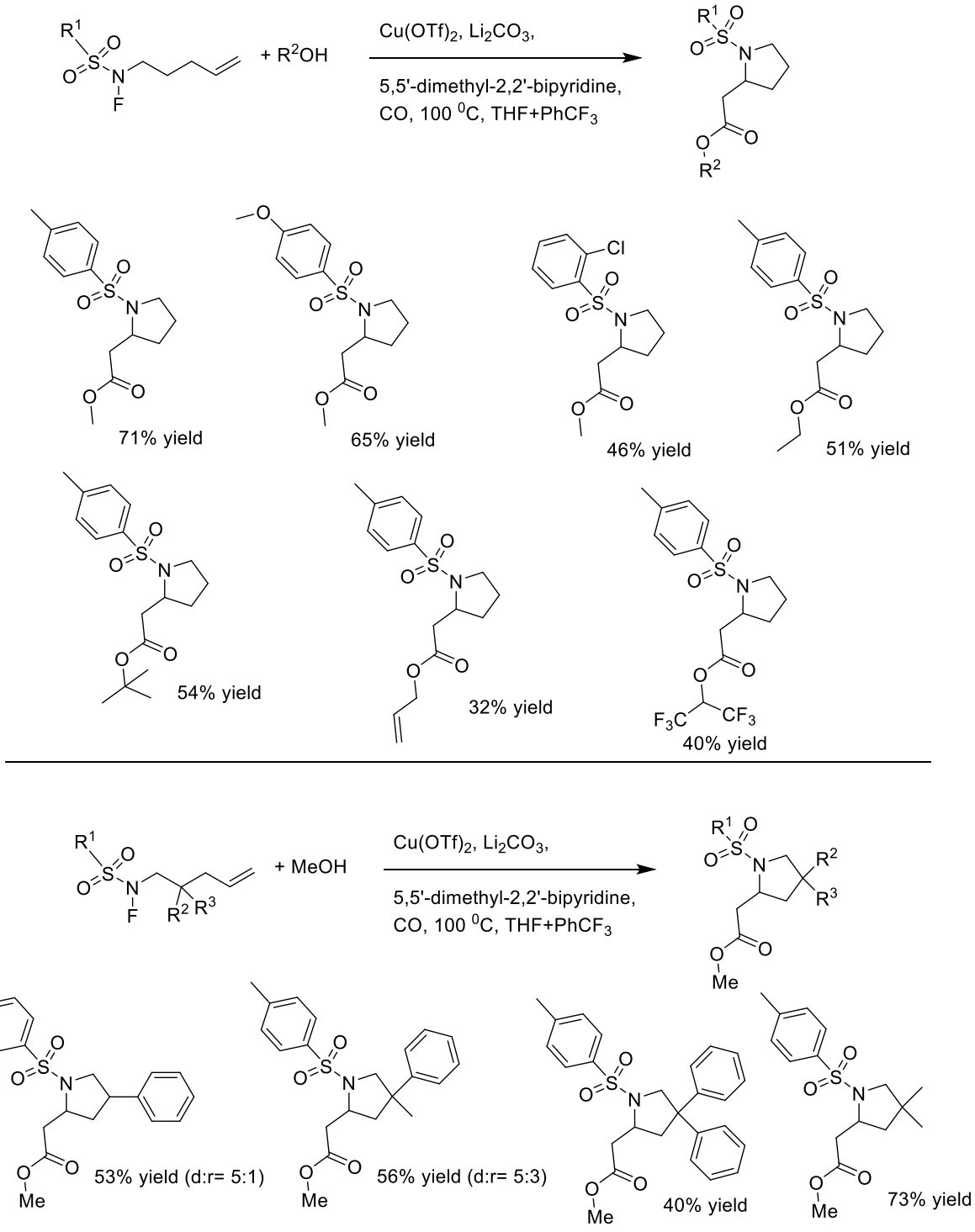


Figure 92. $Cu(OTf)_2/Li_2CO_3$/5,5'-dimethyl-2,2'-bypyridine facilitate N-sulfonyl-β-homoproline esters

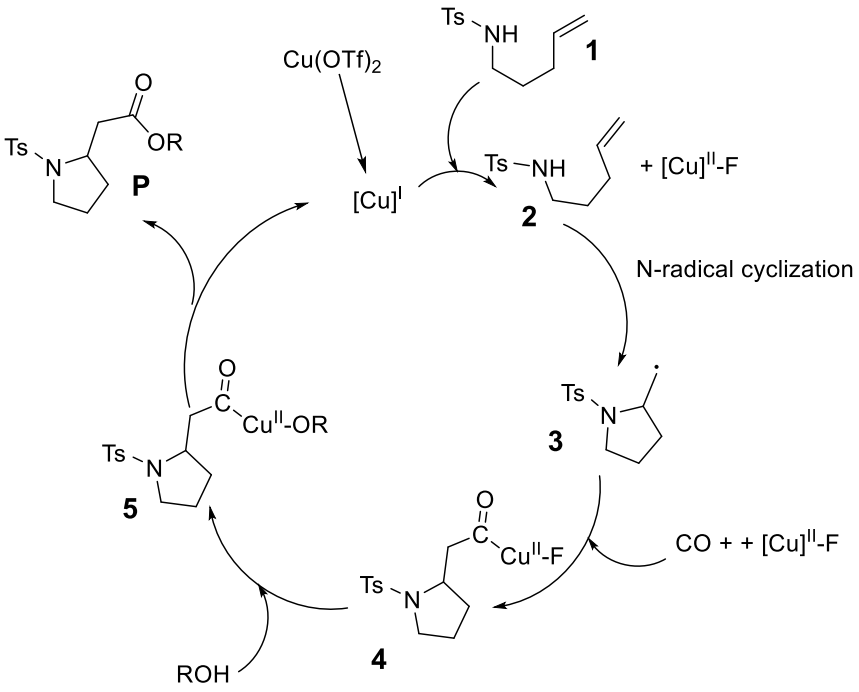


Figure 93. Mechanism studies for the $Cu(OTf)_2/Li_2CO_3$/5,5'-dimethyl-2,2'-bypyridine promoted N-sulfonyl-β-homoproline esters synthesis

4.0. Conclusions and Outlook

To conclude, copper-based homogeneous and heterogeneous catalysts effectively promote the synthesis of sulfonamides. Several synthetic routes have been investigated for the sulfonamides synthesis like C-H/C-X functionalization of aliphatic, alkenes and alkynes by alkyl or arylsulfonyl derivates. Several other functional groups like alcohols, amines, α-,β-unsaturated carbonyl compounds, o-benzoyl hydroxylamines, aromatic and heteroaromatic compounds have also been effectively transformed to the corresponding sulfonamides. Furthermore, multicomponent domino reactions have also been investigated for the synthesis of these sulfonamides.

Synthesis of these sulfonamides has been investigated using the copper-based homogeneous catalytic system; however, heterogeneous copper-based catalysts have been sparsely investigated for the sulfonamides synthesis. Supported copper nanoparticles can be effectively used as the heterogeneous and recyclable catalytic materials for the sulphonamide synthesis. However, size of these copper nanoparticles will be an important parameter in determining the catalytic performance for the sulfonamides synthesis. Reducing the size of the copper nanoparticles can drastically improve the catalytic performance. Therefore,

reducing the size of the metal active sites to the atomic scale can significantly enhance the catalytic performance by generating coordinative unsaturated sites on the catalyst surface. Therefore, for the sustainable manufacturing of these sulfonamides, copper-based heterogeneous recyclable nanocatalysts, single-atom catalysts exhibiting excellent catalytic performance similar to the homogeneous catalysts can be investigated with significant developments in the field. Additionally, the electrochemical and photocatalytic techniques for the synthesis of sulphonamide synthesis have been sparsely investigated. Therefore, modern day synthetic chemists can focus on the synthesis of the advanced materials for the electrochemical and the photocatalytic techniques for the synthesis of these sulfonamides. Furthermore, for the synthesis of these sulphonamides, several sulphur dioxide sources like $K_2S_2O_5$, Na_2SO_5 or DABSO have also been investigated. However, DABSO has proven to be less atom economic SO_2 source. Therefore, more atom economic pathways for the sulfonamides synthesis using sulfinites can be investigated for the sulphonamide synthesis, replacing DABSO as SO_2 surrogate.

5.0. Declarations

Ethical Approval

Not applicable

Competing interests

Not applicable

Authors' contributions

P.C. sincerely thanks all the authors for their kind efforts in writing and revising this manuscript under lockdown situations with all hurdles and well-utilizing work from home time.

Funding

S.M.M. thanks SERB-DST, New Delhi, India (Project CRG/2020/001769), CSIR, New Delhi, India [Project 01(2935)/18/EMR-II], BRNS, Mumbai, India (Project 58/14/17/2020-BRNS/37215), and IIT Indore for financial support. P. C. thankful to MHRD, Government of India for the fellowship, N. C. thanks UGC, New Delhi for the fellowship.

Availability of data and materials

Both print and electronic

6.0. References

1. Supuran, C. T.; Casini, A.; Scozzafava, A., Protease inhibitors of the sulfonamide type: anticancer, antiinflammatory, and antiviral agents. *Medicinal Research Reviews* **2003,** *23* (5), 535-558.
2. Kołaczek, A.; Fusiarz, I.; Ławecka, J.; Branowska, D., Biological activity and synthesis of sulfonamide derivatives: a brief review. *Chemik* **2014,** *68* (7), 620-628.
3. Devendar, P.; Yang, G.-F., Sulfur-containing agrochemicals. *Sulfur Chemistry* **2019**, 35-78.
4. Sondhi, S. M.; Rani, R.; Roy, P.; Agrawal, S.; Saxena, A., Synthesis, anti-inflammatory, and anticancer activity evaluation of some heterocyclic amidine and bis-amidine derivatives. *Journal of Heterocyclic Chemistry* **2011,** *48* (4), 921-926.
5. Potgieter, K. C., Rhenium complexes with multidentate benzazoles and related N, X-donor (X= N, O, S) ligands. **2012**.
6. Bahekar, S. S.; Shinde, D. B., Synthesis and anti-inflammatory activity of some [4,6-(4-substituted aryl)-2-thioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl]-acetic acid derivatives. *Bioorganic & Medicinal Chemistry Letters* **2004,** *14* (7), 1733-1736.
7. Taylor, E. C.; Liu, B., A new and efficient synthesis of pyrrolo [2, 3-d] pyrimidine anticancer agents: alimta (LY231514, MTA), homo-alimta, TNP-351, and some aryl 5-substituted pyrrolo [2, 3-d] pyrimidines. *The Journal of Organic Chemistry* **2003,** *68* (26), 9938-9947.
8. Huang, S.-T.; Hsei, I.-J.; Chen, C., Synthesis and anticancer evaluation of bis (benzimidazoles), bis (benzoxazoles), and benzothiazoles. *Bioorganic & medicinal chemistry* **2006,** *14* (17), 6106-6119.
9. Anzini, M.; Chelini, A.; Mancini, A.; Cappelli, A.; Frosini, M.; Ricci, L.; Valoti, M.; Magistretti, J.; Castelli, L.; Giordani, A., Synthesis and biological evaluation of amidine, guanidine, and thiourea derivatives of 2-amino (6-trifluoromethoxy) benzothiazole as neuroprotective agents potentially useful in brain diseases. *Journal of medicinal chemistry* **2010,** *53* (2), 734-744.
10. Verma, S. K.; Verma, R.; Xue, F.; Thakur, P. K.; Girish, Y.; Rakesh, K., Antibacterial activities of sulfonyl or sulfonamide containing heterocyclic derivatives and its structure-activity relationships (SAR) studies: A critical review. *Bioorganic Chemistry* **2020,** *105*, 104400.

11. Mondal, S.; Malakar, S., Synthesis of sulfonamide and their synthetic and therapeutic applications: Recent advances. *Tetrahedron* **2020,** *76* (48), 131662.

12. Joseph, D.; Idris, M. A.; Chen, J.; Lee, S., Recent advances in the catalytic synthesis of arylsulfonyl compounds. *ACS Catalysis* **2021,** *11* (7), 4169-4204.

13. Scozzafava, A.; Menabuoni, L.; Mincione, F.; Briganti, F.; Mincione, G.; Supuran, C. T., Carbonic anhydrase inhibitors: perfluoroalkyl/aryl-substituted derivatives of aromatic/heterocyclic sulfonamides as topical intraocular pressure-lowering agents with prolonged duration of action. *Journal of medicinal chemistry* **2000,** *43* (23), 4542-4551.

14. Scozzafava, A.; Menabuoni, L.; Mincione, F.; Supuran, C. T., Carbonic anhydrase inhibitors. A general approach for the preparation of water-soluble sulfonamides incorporating polyamino− polycarboxylate tails and of their metal complexes possessing long-lasting, topical intraocular pressure-lowering properties. *Journal of medicinal chemistry* **2002,** *45* (7), 1466-1476.

15. Pacchiano, F.; Aggarwal, M.; Avvaru, B. S.; Robbins, A. H.; Scozzafava, A.; McKenna, R.; Supuran, C. T., Selective hydrophobic pocket binding observed within the carbonic anhydrase II active site accommodate different 4-substituted-ureido-benzenesulfonamides and correlate to inhibitor potency. *Chemical Communications* **2010,** *46* (44), 8371-8373.

16. Moriggi, J.-D.; Brown, L. J.; Castro, J. L.; Brown, R. C., Ring-closing metathesis: development of a cyclisation–cleavage strategy for the solid-phase synthesis of cyclic sulfonamides. *Organic & Biomolecular Chemistry* **2004,** *2* (6), 835-844.

17. Tummanapalli, S.; Bodige, S.; Gulipalli, K. C.; Endoori, S.; Medaboina, S.; Mallidi, K., Direct sulfonylamidation of unfunctionalized arenes in CH activation manner: A simple protocol to access primary sulfonamides. *Tetrahedron Letters* **2022,** *97*, 153781.

18. Kerr, W. J.; Reid, M.; Tuttle, T., Iridium-catalyzed C–H activation and deuteration of primary sulfonamides: an experimental and computational study. *ACS Catalysis* **2015,** *5* (1), 402-410.

19. Lou, T. S. B.; Bagley, S. W.; Willis, M. C., Cyclic Alkenylsulfonyl Fluorides: Palladium-Catalyzed Synthesis and Functionalization of Compact Multifunctional Reagents. *Angewandte Chemie* **2019,** *131* (52), 19035-19039.

20. Gioiello, A.; Rosatelli, E.; Teofrasti, M.; Filipponi, P.; Pellicciari, R., Building a sulfonamide library by eco-friendly flow synthesis. *ACS Combinatorial Science* **2013,** *15* (5), 235-239.

21. Wydysh, E. A.; Medghalchi, S. M.; Vadlamudi, A.; Townsend, C. A., Design and synthesis of small molecule glycerol 3-phosphate acyltransferase inhibitors. *Journal of medicinal chemistry* **2009,** *52* (10), 3317-3327.

22. Joseph, D.; Idris, M. A.; Chen, J.; Lee, S., Recent Advances in the Catalytic Synthesis of Arylsulfonyl Compounds. *ACS Catalysis* **2021,** *11*, 4169-4204.

23. Kitajima, N.; Moro-oka, Y., Copper-dioxygen complexes. Inorganic and bioinorganic perspectives. *Chemical Reviews* **1994,** *94* (3), 737-757.

24. Liu, X.; Zhang, Y.; Wang, L.; Fu, H.; Jiang, Y.; Zhao, Y., General and Efficient Copper-Catalyzed Amidation of Saturated C−H Bonds Using N-Halosuccinimides as the Oxidants. *The Journal of Organic Chemistry* **2008,** *73* (16), 6207-6212.

25. Lee, D.; Kim, S. M.; Hirao, H.; Hong, S. H., Gold (I)/Gold (III)-catalyzed selective synthesis of N-sulfonyl enaminone isomers from sulfonamides and ynones via two distinct reaction pathways. *Organic letters* **2017,** *19* (18), 4734-4737.

26. Liang, X.; Huang, X.; Xiong, M.; Shen, K.; Pan, Y., Copper (i)-catalyzed N–H olefination of sulfonamides for N-sulfonyl enaminone synthesis. *Chemical Communications* **2018,** *54* (60), 8403-8406.

27. Kondo, T.; Yoshida, K.; Yoshimura, Y.; Tanayama, S., Enantioselective pharmacokinetics in animals of pazinaclone, a new isoindoline anxiolytic, and its active metabolite. *Biopharmaceutics & Drug Disposition* **1995,** *16* (9), 755-773.

28. Mertens, A.; Zilch, H.; Koenig, B.; Schaefer, W.; Poll, T.; Kampe, W.; Seidel, H.; Leser, U.; Leinert, H., Selective non-nucleoside HIV-1 reverse transcriptase inhibitors. New 2,3-dihydrothiazolo[2,3-a]isoindol-5(9bH)-ones and related compounds with anti-HIV-1 activity. *Journal of Medicinal Chemistry* **1993,** *36* (17), 2526-2535.

29. Armoiry, X.; Aulagner, G.; Facon, T., Lenalidomide in the treatment of multiple myeloma: a review. *Journal of clinical pharmacy and therapeutics* **2008,** *33* (3), 219-226.

30. Augner, D.; Krut, O.; Slavov, N.; Gerbino, D. C.; Sahl, H.-G.; Benting, J.; Nising, C. F.; Hillebrand, S.; Krönke, M.; Schmalz, H.-G., On the Antibiotic and Antifungal Activity of Pestalone, Pestalachloride A, and Structurally Related Compounds. *Journal of Natural Products* **2013,** *76* (8), 1519-1522.

31. Speck, K.; Magauer, T., The chemistry of isoindole natural products. *Beilstein Journal of Organic Chemistry* **2013,** *9*, 2048-2078.

32. Bedford, R. B.; Bowen, J. G.; Méndez-Gálvez, C., Isoindolinones via Copper-Catalyzed Intramolecular Benzylic C–H Sulfamidation. *The Journal of Organic Chemistry* **2017,** *82* (3), 1719-1725.

33. Powell, D. A.; Fan, H., Copper-Catalyzed Amination of Primary Benzylic C−H Bonds with Primary and Secondary Sulfonamides. *The Journal of Organic Chemistry* **2010,** *75* (8), 2726-2729.

34. Pelletier, G.; Powell, D. A., Copper-Catalyzed Amidation of Allylic and Benzylic CH Bonds. *Organic Letters* **2006,** *8* (26), 6031-6034.

35. Kwong, H.-L.; Liu, D.; Chan, K.-Y.; Lee, C.-S.; Huang, K.-H.; Che, C.-M., Copper(I)-catalyzed asymmetric alkene aziridination mediated by PhI(OAc)2: a facile one-pot procedure. *Tetrahedron Letters* **2004,** *45* (20), 3965-3968.

36. Pansare, S. V.; Pandya, K., Simple diamine-and triamine-protonic acid catalysts for the enantioselective Michael addition of cyclic ketones to nitroalkenes. *Journal of the American Chemical Society* **2006,** *128* (30), 9624-9625.

37. Zhou, Y.; Zhu, Y.; Yan, S.; Gong, Y., Copper-Catalyzed Enantioselective Henry Reaction of Enals and Subsequent Iodocyclization: Stereoselective Construction of Chiral Azatricyclic Frameworks. *Angewandte Chemie International Edition* **2013,** *52* (39), 10265-10269.

38. Turnpenny, B. W.; Chemler, S. R., Copper-catalyzed alkene diamination: synthesis of chiral 2-aminomethyl indolines and pyrrolidines. *Chemical Science* **2014,** *5* (5), 1786-1793.

39. Wang, Y.; Deng, L.; Zhou, J.; Wang, X.; Mei, H.; Han, J.; Pan, Y., Synthesis of Chiral Sulfonyl Lactones via Copper-Catalyzed Asymmetric Radical Reaction of DABCO·(SO2). *Advanced Synthesis & Catalysis* **2018,** *360* (6), 1060-1065.

40. Levy, L., Drugs of the future. *Drugs Future* **1992,** *17*, 451.

41. Dauban, P.; Dodd, R. H., Synthesis of Cyclic Sulfonamides via Intramolecular Copper-Catalyzed Reaction of Unsaturated Iminoiodinanes. *Organic Letters* **2000,** *2* (15), 2327-2329.

42. Wroblewski, T.; Graul, A.; Castaner, J., BRINZOLAMIDE: ANTIGLAUCOMA CARBONIC ANHYDRASE INHIBITOR. *Drugs of the Future* **1998,** *23* (4), 365-369.

43. Silver, L., The Brinzolamide Primary Therapy Study Group: Clinical efficacy and safety of brinzolamide (Azopt), a new topical carbonic anhydrase inhibitor for primary open-angle glaucoma and ocular hypertension. *Am J Ophthalmol* **1998,** *126* (3), 400-408.

44. Kaneko, K.; Yoshino, T.; Matsunaga, S.; Kanai, M., Sultam synthesis via Cu-catalyzed intermolecular carboamination of alkenes with N-fluorobenzenesulfonimide. *Organic letters* **2013,** *15* (10), 2502-2505.

45. Wells, G. J.; Tao, M.; Josef, K. A.; Bihovsky, R., 1,2-Benzothiazine 1,1-Dioxide P2−P3 Peptide Mimetic Aldehyde Calpain I Inhibitors. *Journal of Medicinal Chemistry* **2001,** *44* (21), 3488-3503.

46. Ingram, C. J.; Brubaker, R. F., Effect of brinzolamide and dorzolamide on aqueous humor flow in human eyes. *American journal of ophthalmology* **1999,** *128* (3), 292-296.

47. Bergmeier, S. C., The synthesis of vicinal amino alcohols. *Tetrahedron* **2000,** *17* (56), 2561-2576.

48. Donohoe, T. J.; Callens, C. K.; Flores, A.; Lacy, A. R.; Rathi, A. H., Recent developments in methodology for the direct oxyamination of olefins. *Chemistry–A European Journal* **2011,** *17* (1), 58-76.

49. Paderes, M. C.; Keister, J. B.; Chemler, S. R., Mechanistic Analysis and Optimization of the Copper-Catalyzed Enantioselective Intramolecular Alkene Aminooxygenation. *The Journal of Organic Chemistry* **2013,** *78* (2), 506-515.

50. Owa, T.; Yoshino, H.; Okauchi, T.; Yoshimatsu, K.; Ozawa, Y.; Sugi, N. H.; Nagasu, T.; Koyanagi, N.; Kitoh, K., Discovery of novel antitumor sulfonamides targeting G1 phase of the cell cycle. *Journal of medicinal chemistry* **1999,** *42* (19), 3789-3799.

51. Gilbert, A. M.; Caltabiano, S.; Koehn, F. E.; Chen, Z.-j.; Francisco, G. D.; Ellingboe, J. W.; Kharode, Y.; Mangine, A.; Francis, R.; TrailSmith, M.; Gralnick, D., Pyrazolopyrimidine-2,4-dione Sulfonamides: Novel and Selective Calcitonin Inducers. *Journal of Medicinal Chemistry* **2002,** *45* (11), 2342-2345.

52. Taylor, J. G.; Whittall, N.; Hii, K. K., Copper-Catalyzed Intermolecular Hydroamination of Alkenes. *Organic Letters* **2006,** *8* (16), 3561-3564.

53. Jung, N.; Bräse, S., Vinyl and Alkynyl Azides: Well-Known Intermediates in the Focus of Modern Synthetic Methods. *Angewandte Chemie International Edition* **2012,** *51* (49), 12169-12171.

54. Scriven, E. F. V.; Turnbull, K., Azides: their preparation and synthetic uses. *Chemical Reviews* **1988,** *88* (2), 297-368.

55. Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V., Organic azides: an exploding diversity of a unique class of compounds. *Angewandte Chemie International Edition* **2005,** *44* (33), 5188-5240.

56. Park, C.; Kim, H.; Kim, S.; Kim, C., Enzyme Responsive Nanocontainers with Cyclodextrin Gatekeepers and Synergistic Effects in Release of Guests. *Journal of the American Chemical Society* **2009,** *131* (46), 16614-16615.

57. Zhang, B.; Studer, A., Copper-Catalyzed Intermolecular Aminoazidation of Alkenes. *Organic Letters* **2014,** *16* (6), 1790-1793.

58. Zhang, H.; Pu, W.; Xiong, T.; Li, Y.; Zhou, X.; Sun, K.; Liu, Q.; Zhang, Q., Copper-Catalyzed Intermolecular Aminocyanation and Diamination of Alkenes. *Angewandte Chemie International Edition* **2013,** *52* (9), 2529-2533.

59. Liwosz, T. W.; Chemler, S. R., Copper-Catalyzed Enantioselective Intramolecular Alkene Amination/Intermolecular Heck-Type Coupling Cascade. *Journal of the American Chemical Society* **2012,** *134* (4), 2020-2023.

60. Chang, J. W. W.; Ton, T. M. U.; Tania, S.; Taylor, P. C.; Chan, P. W. H., Practical copper(i)-catalysed amidation of aldehydes. *Chemical Communications* **2010,** *46* (6), 922-924.

61. Li, G.; Wei, H.-X.; Kim, S. H., Copper-Catalyzed Aminohalogenation Using the 2-NsNCl2/2-NsNHNa Combination as the Nitrogen and Halogen Sources for the Synthesis of anti-Alkyl 3-Chloro-2-(o-nitrobenzenesulfonamido)-3-arylpropionates. *Organic Letters* **2000,** *2* (15), 2249-2252.

62. Pouambeka, T. W.; Zhang, G.; Zheng, G.-F.; Xu, G.-X.; Zhang, Q.; Xiong, T., Copper-catalyzed oxidative amidation of α, β-unsaturated ketones via selective C–H or C–C bond cleavage. *Organic Chemistry Frontiers* **2017,** *4* (7), 1420-1424.

63. Li, G.; Wei, H.-X.; Kim, S. H., Unexpected copper-catalyzed aminohalogenation reaction of olefins using N-halo-N-metallo-sulfonamide as the nitrogen and halogen sources. *Tetrahedron* **2001,** *57* (40), 8407-8411.

64. Matsubara, R.; Doko, T.; Uetake, R.; Kobayashi, S., Enesulfonamides as Nucleophiles in Catalytic Asymmetric Reactions. *Angewandte Chemie International Edition* **2007,** *46* (17), 3047-3050.

65. Harrison, T. J.; Dake, G. R., Pt (II) or Ag (I) salt catalyzed cycloisomerizations and tandem cycloadditions forming functionalized azacyclic arrays. *Organic Letters* **2004,** *6* (26), 5023-5026.

66. Harrison, T. J.; Patrick, B. O.; Dake, G. R., Platinum (II)-catalyzed cyclizations forming quaternary carbon centers, using enesulfonamides, enecarbamates, or enamides as nucleophiles. *Organic Letters* **2007,** *9* (2), 367-370.

67. Liu, X.-Y.; Gao, P.; Shen, Y.-W.; Liang, Y.-M., Copper-Catalyzed Chloroamination of Alkynes: Highly Regio- and Stereoselective Synthesis of (E)-β-Chloro-Enesulfonamides. *Advanced Synthesis & Catalysis* **2011,** *353* (17), 3157-3160.

68. Reidl, T. W.; Anderson, L. L., Divergent Functionalizations of Azetidines and Unsaturated Azetidines. *Asian Journal of Organic Chemistry* **2019,** *8* (7), 931-945.

69. Whiting, M.; Fokin, V. V., Copper-Catalyzed Reaction Cascade: Direct Conversion of Alkynes into N-Sulfonylazetidin-2-imines. *Angewandte Chemie International Edition* **2006,** *45* (19), 3157-3161.

70. Cassidy, M. P.; Raushel, J.; Fokin, V. V., Practical Synthesis of Amides from In Situ Generated Copper(I) Acetylides and Sulfonyl Azides. *Angewandte Chemie International Edition* **2006,** *45* (19), 3154-3157.

71. Cheng, G.; Cui, X., Efficient Approach to 4-Sulfonamidoquinolines via Copper(I)-Catalyzed Cascade Reaction of Sulfonyl Azides with Alkynyl Imines. *Organic Letters* **2013,** *15* (7), 1480-1483.

72. Shang, Y.; He, X.; Hu, J.; Wu, J.; Zhang, M.; Yu, S.; Zhang, Q., Copper-Catalyzed Efficient Multicomponent Reaction: Synthesis of Benzoxazoline-Amidine Derivatives. *Advanced Synthesis & Catalysis* **2009,** *351* (16), 2709-2713.

73. Yavari, I.; Ahmadian, S.; Ghazanfarpur-Darjani, M.; Solgi, Y., Formation of N-sulfonylamidines by copper-catalyzed coupling of sulfonyl azides, terminal alkynes, and trialkylamines. *Tetrahedron Letters* **2011,** *52* (6), 668-670.

74. Hiroya, K.; Itoh, S.; Sakamoto, T., Development of an Efficient Procedure for Indole Ring Synthesis from 2-Ethynylaniline Derivatives Catalyzed by Cu(II) Salts and Its Application to Natural Product Synthesis. *The Journal of Organic Chemistry* **2004,** *69* (4), 1126-1136.

75. Zhang, P.; Cook, A. M.; Liu, Y.; Wolf, C., Copper(I)-Catalyzed Nucleophilic Addition of Ynamides to Acyl Chlorides and Activated N-Heterocycles. *The Journal of Organic Chemistry* **2014,** *79* (9), 4167-4173.

76. More, V. D.; Choudhari, P. B.; Dhavale, R. P.; Jadhav, S. D.; Bhatia, M. S., 3D QSAR study on alpha keto amide derivatives as gp120-CD4 inhibitors. *Int J Pharm Sci Drug Res* **2012,** *4*, 19-24.

77. Robello, M.; Barresi, E.; Baglini, E.; Salerno, S.; Taliani, S.; Settimo, F. D., The alpha keto amide moiety as a privileged motif in medicinal chemistry: current insights and emerging opportunities. *Journal of Medicinal Chemistry* **2021,** *64* (7), 3508-3545.

78. Cooper, A. J.; Ginos, J. Z.; Meister, A., Synthesis and properties of the. alpha.-keto acids. *Chemical Reviews* **1983,** *83* (3), 321-358.

79. Ragupathi, A.; Charpe, V. P.; Sagadevan, A.; Hwang, K. C., Visible Light-Mediated Copper (I)-Catalysed Aerobic Oxidation of Ynamides/Ynamines at Room Temperature: A

Sustainable Approach to the Synthesis of α-Ketoimides/α-Ketoamides. *Advanced Synthesis & Catalysis* **2017,** *359* (7), 1138-1143.

80. Cho, S. H.; Yoo, E. J.; Bae, I.; Chang, S., Copper-Catalyzed Hydrative Amide Synthesis with Terminal Alkyne, Sulfonyl Azide, and Water. *Journal of the American Chemical Society* **2005,** *127* (46), 16046-16047.

81. Cho, S. H.; Chang, S., Rate-Accelerated Nonconventional Amide Synthesis in Water: A Practical Catalytic Aldol-Surrogate Reaction. *Angewandte Chemie International Edition* **2007,** *46* (11), 1897-1900.

82. Zhang, Y.; Hsung, R. P.; Tracey, M. R.; Kurtz, K. C. M.; Vera, E. L., Copper Sulfate-Pentahydrate-1,10-Phenanthroline Catalyzed Amidations of Alkynyl Bromides. Synthesis of Heteroaromatic Amine Substituted Ynamides. *Organic Letters* **2004,** *6* (7), 1151-1154.

83. Taniguchi, N., Copper-Catalyzed Oxidative Synthesis of Sulfinamides Using Thiols or Disulfides with Amines. *European Journal of Organic Chemistry* **2016,** *2016* (12), 2157-2162.

84. Cui, X.; Shi, F.; Tse, M. K.; Gördes, D.; Thurow, K.; Beller, M.; Deng, Y., Copper-Catalyzed N-Alkylation of Sulfonamides with Benzylic Alcohols: Catalysis and Mechanistic Studies. *Advanced Synthesis & Catalysis* **2009,** *351* (17), 2949-2958.

85. Shi, F.; Tse, M. K.; Cui, X.; Gördes, D.; Michalik, D.; Thurow, K.; Deng, Y.; Beller, M., Copper-Catalyzed Alkylation of Sulfonamides with Alcohols. *Angewandte Chemie International Edition* **2009,** *48* (32), 5912-5915.

86. Li, Q.; Fan, S.; Sun, Q.; Tian, H.; Yu, X.; Xu, Q., Copper-catalyzed N-alkylation of amides and amines with alcohols employing the aerobic relay race methodology. *Organic & Biomolecular Chemistry* **2012,** *10* (15), 2966-2972.

87. Huang, X.; Wang, J.; Ni, Z.; Wang, S.; Pan, Y., Copper-mediated S–N formation via an oxygen-activated radical process: a new synthesis method for sulfonamides. *Chemical Communications* **2014,** *50* (35), 4582-4584.

88. Tang, X.; Huang, L.; Qi, C.; Wu, X.; Wu, W.; Jiang, H., Copper-catalyzed sulfonamides formation from sodium sulfinates and amines. *Chemical Communications* **2013,** *49* (54), 6102-6104.

89. Du, B.; Wang, Y.; Sha, W.; Qian, P.; Mei, H.; Han, J.; Pan, Y., Copper-Catalyzed Selective Aerobic Oxidative Cascade Reaction of Hydrazines, DABSO, and Amines for the Direct Synthesis of Sulfonamides. *Asian Journal of Organic Chemistry* **2017,** *6* (2), 153-156.

90. Chung, S.; Kim, J., Cu-catalyzed aerobic oxidative synthesis of sulfonamides from sulfonyl hydrazides and amines. *Tetrahedron Letters* **2019,** *60* (11), 792-795.

91. Fukudome, Y.; Naito, H.; Hata, T.; Urabe, H., Copper-Catalyzed 1,2-Double Amination of 1-Halo-1-alkynes. Concise Synthesis of Protected Tetrahydropyrazines and Related Heterocyclic Compounds. *Journal of the American Chemical Society* **2008,** *130* (6), 1820-1821.

92. Ley, S. V.; Thomas, A. W., Modern Synthetic Methods for Copper-Mediated C(aryl)□O, C(aryl)□N, and C(aryl)□S Bond Formation. *Angewandte Chemie International Edition* **2003,** *42* (44), 5400-5449.

93. Lam, P. Y. S.; Vincent, G.; Clark, C. G.; Deudon, S.; Jadhav, P. K., Copper-catalyzed general C□N and C□O bond cross-coupling with arylboronic acid. *Tetrahedron Letters* **2001,** *42* (20), 3415-3418.

94. Schlummer, B.; Scholz, U., Palladium-Catalyzed C□N and C□O Coupling–A Practical Guide from an Industrial Vantage Point†. *Advanced Synthesis & Catalysis* **2004,** *346* (13-15), 1599-1626.

95. Muci, A. R.; Buchwald, S. L., Practical palladium catalysts for CN and CO bond formation. *Cross-Coupling Reactions* **2002**, 131-209.

96. Lan, J.-B.; Zhang, G.-L.; Yu, X.-Q.; You, J.-S.; Chen, L.; Yan, M.; Xie, R.-G., A simple copper salt catalyzed N-arylation of amines, amides, imides, and sulfonamides with arylboronic acids. *Synlett* **2004,** *2004* (06), 1095-1097.

97. Teo, Y.-C.; Yong, F.-F., Efficient ligand-free, copper-catalyzed N-arylation of sulfonamides. *Synlett* **2011,** *2011* (06), 837-843.

98. Lu, H.; Yuan, X.; Zhu, S.; Sun, C.; Li, C., Copper-Catalyzed Intramolecular N-Vinylation of Sulfonamides: General and Efficient Synthesis of Heterocyclic Enamines and Macrolactams. *The Journal of Organic Chemistry* **2008,** *73* (21), 8665-8668.

99. Rao, R. K.; Naidu, A. B.; Sekar, G., Highly Efficient Copper-Catalyzed Domino Ring Opening and Goldberg Coupling Cyclization for the Synthesis of 3,4-Dihydro-2H-1,4-benzoxazines. *Organic Letters* **2009,** *11* (9), 1923-1926.

100. Chen, Y.; Murray, P. R. D.; Davies, A. T.; Willis, M. C., Direct Copper-Catalyzed Three-Component Synthesis of Sulfonamides. *Journal of the American Chemical Society* **2018,** *140* (28), 8781-8787.

101. Loukrakpam, D. C.; Phukan, P., CuI catalyzed sulfamidation of arylboronic acid using TsNBr2 at room temperature. *Tetrahedron Letters* **2017,** *58* (52), 4855-4858.

102. John, A.; Nicholas, K. M., Copper-Catalyzed Amidation of 2-Phenylpyridine with Oxygen as the Terminal Oxidant. *The Journal of Organic Chemistry* **2011,** *76* (10), 4158-4162.

103. He, H.; Wu, Y.-J., Copper-catalyzed N-arylation of sulfonamides with aryl bromides and iodides using microwave heating. *Tetrahedron Letters* **2003,** *44* (16), 3385-3386.

104. Deng, W.; Liu, L.; Zhang, C.; Liu, M.; Guo, Q.-X., Copper-catalyzed cross-coupling of sulfonamides with aryl iodides and bromides facilitated by amino acid ligands. *Tetrahedron Letters* **2005,** *46* (43), 7295-7298.

105. Miyasaka, M.; Hirano, K.; Satoh, T.; Kowalczyk, R.; Bolm, C.; Miura, M., Copper-Catalyzed Direct Sulfoximination of Azoles and Polyfluoroarenes under Ambient Conditions. *Organic Letters* **2011,** *13* (3), 359-361.

106. Ji, J.; Liu, Z.; Liu, P.; Sun, P., Synthesis of sulfonamides via copper-catalyzed oxidative C–N bond cleavage of tertiary amines. *Organic & Biomolecular Chemistry* **2016,** *14* (29), 7018-7023.

107. Han, X., Cross coupling of 3-bromopyridine and sulfonamides (R1NHSO2R2·R1=H, Me, alkyl; R2=alkyl and aryl) catalyzed by CuI/1,3-di(pyridin-2-yl)propane-1,3-dione. *Tetrahedron Letters* **2010,** *51* (2), 360-362.

108. Wang, X.; Guram, A.; Ronk, M.; Milne, J. E.; Tedrow, J. S.; Faul, M. M., Copper-catalyzed N-arylation of sulfonamides with aryl bromides under mild conditions. *Tetrahedron Letters* **2012,** *53* (1), 7-10.

109. Wang, S.; Ni, Z.; Huang, X.; Wang, J.; Pan, Y., Copper-Catalyzed Direct Amidation of Heterocycles with N-Fluorobenzenesulfonimide. *Organic Letters* **2014,** *16* (21), 5648-5651.

110. Baffoe, J.; Hoe, M. Y.; Touré, B. B., Copper-Mediated N-Heteroarylation of Primary Sulfonamides: Synthesis of Mono-N-heteroaryl Sulfonamides. *Organic Letters* **2010,** *12* (7), 1532-1535.

111. Sayyad, M.; Nanaji, Y.; Ghorai, M. K., A Synthetic Route to 2-Alkyl Indoles via Thiophenol-Mediated Ring-Opening of N-Tosylaziridines Followed by Copper Powder-Mediated C–N Cyclization/Aromatization. *The Journal of Organic Chemistry* **2015,** *80* (24), 12659-12667.

112. Yu, H.; Li, Z.; Bolm, C., Copper-Catalyzed Transsulfinamidation of Sulfinamides as a Key Step in the Preparation of Sulfonamides and Sulfonimidamides. *Angewandte Chemie International Edition* **2018,** *57* (47), 15602-15605.

113. Zhu, H.; Shen, Y.; Deng, Q.; Tu, T., Copper-catalyzed electrophilic amination of sodium sulfinates at room temperature. *Chemical Communications* **2015,** *51* (92), 16573-16576.

114. Sabat, N.; Klečka, M.; Slavětínská, L.; Klepetářová, B.; Hocek, M., Direct C–H amination and C–H chloroamination of 7-deazapurines. *RSC Advances* **2014,** *4* (107), 62140-62143.

115. Ohta, Y.; Chiba, H.; Oishi, S.; Fujii, N.; Ohno, H., Construction of Nitrogen Heterocycles Bearing an Aminomethyl Group by Copper-Catalyzed Domino Three-Component Coupling−Cyclization. *The Journal of Organic Chemistry* **2009,** *74* (18), 7052-7058.

116. You, C.; Yao, F.; Yan, T.; Cai, M., A highly efficient heterogeneous copper-catalyzed Chan–Lam coupling reaction of sulfonyl azides with arylboronic acids leading to N-arylsulfonamides. *RSC Advances* **2016,** *6* (49), 43605-43612.

117. Fang, S.; Zhao, Y.; Li, H.; Zheng, Y.; Lian, P.; Wan, X., [3 + 3]-Cycloaddition of α-Diazocarbonyl Compounds and N-Tosylaziridines: Synthesis of Polysubstituted 2H-1,4-Oxazines through Synergetic Catalysis of AgOTf/Cu(OAc)2. *Organic Letters* **2019,** *21* (7), 2356-2359.

118. Yim, C.-B.; Dijkgraaf, I.; Merkx, R.; Versluis, C.; Eek, A.; Mulder, G. E.; Rijkers, D. T. S.; Boerman, O. C.; Liskamp, R. M. J., Synthesis of DOTA-Conjugated Multimeric [Tyr3]Octreotide Peptides via a Combination of Cu(I)-Catalyzed "Click" Cycloaddition and Thio Acid/Sulfonyl Azide "Sulfo-Click" Amidation and Their in Vivo Evaluation. *Journal of Medicinal Chemistry* **2010,** *53* (10), 3944-3953.

119. Yang, W.; Huang, D.; Zeng, X.; Zhang, J.; Wang, X.; Hu, Y., N-Sulfonyl acetylketenimine as a highly reactive intermediate for synthesis of N-Aroylsulfonamides. *Tetrahedron* **2019,** *75* (3), 381-386.

120. Boovanahalli, S. K.; Jin, X.; Jin, Y.; Kim, J. H.; Dat, N. T.; Hong, Y.-S.; Lee, J. H.; Jung, S.-H.; Lee, K.; Lee, J. J., Synthesis of (aryloxyacetylamino)-isonicotinic/nicotinic acid analogues as potent hypoxia-inducible factor (HIF)-1α inhibitors. *Bioorganic & medicinal chemistry letters* **2007,** *17* (22), 6305-6310.

121. Nagarajan, S. R.; Devadas, B.; Malecha, J. W.; Lu, H.-F.; Ruminski, P. G.; Rico, J. G.; Rogers, T. E.; Marrufo, L. D.; Collins, J. T.; Kleine, H. P., R-isomers of Arg-Gly-Asp (RGD) mimics as potent αvβ3 inhibitors. *Bioorganic & medicinal chemistry* **2007,** *15* (11), 3783-3800.

122. Shaw, D. E.; Baig, F.; Bruce, I.; Chamoin, S.; Collingwood, S. P.; Cross, S.; Dayal, S.; Drückes, P.; Furet, P.; Furminger, V., Optimization of platelet-derived growth factor receptor (PDGFR) inhibitors for duration of action, as an inhaled therapy for lung remodeling in pulmonary arterial hypertension. *Journal of Medicinal Chemistry* **2016,** *59* (17), 7901-7914.

123. Ibrahim, H. M.; Behbehani, H.; Elnagdi, M. H., Approaches towards the synthesis of a novel class of 2-amino-5-arylazonicotinate, pyridazinone and pyrido [2, 3-d] pyrimidine derivatives as potent antimicrobial agents. *Chemistry Central Journal* **2013,** *7* (1), 1-16.

124. Reddy, C. R.; Prajapti, S. K.; Ranjan, R., Cu(I)-Catalyzed Aminative Aza-Annulation of Enynyl Azide using N-Fluorobenzenesulfonimide: Synthesis of 5-Aminonicotinates. *Organic Letters* **2018,** *20* (10), 3128-3131.

125. Kaminski, J. J.; Puchalski, C.; Solomon, D. M.; Rizvi, R. K.; Conn, D. J.; Elliott, A. J.; Lovey, R. G.; Guzik, H.; Chiu, P., Antiulcer agents. 4. Conformational considerations and the antiulcer activity of substituted imidazo [1, 2-a] pyridines and related analogs. *Journal of medicinal chemistry* **1989,** *32* (8), 1686-1700.

126. Park, S.; Kim, H.; Son, J.-Y.; Um, K.; Lee, S.; Baek, Y.; Seo, B.; Lee, P. H., Synthesis of Imidazopyridines via Copper-Catalyzed, Formal Aza-[3 + 2] Cycloaddition Reaction of Pyridine Derivatives with α-Diazo Oxime Ethers. *The Journal of Organic Chemistry* **2017,** *82* (19), 10209-10218.

127. Du, B.; Shan, A.; Zhong, X.; Zhang, Y.; Chen, D.; Cai, K., Zolpidem arouses patients in vegetative state after brain injury: quantitative evaluation and indications. *The American journal of the medical sciences* **2014,** *347* (3), 178-182.

128. Huo, C.; Tang, J.; Xie, H.; Wang, Y.; Dong, J., CBr4 mediated oxidative C–N bond formation: applied in the synthesis of Imidazo [1, 2-α] pyridines and Imidazo [1, 2-α] pyrimidines. *Organic letters* **2016,** *18* (5), 1016-1019.

129. Lu, S.; Tian, L.-L.; Cui, T.-W.; Zhu, Y.-S.; Zhu, X.; Hao, X.-Q.; Song, M.-P., Copper-Mediated C–H Amination of Imidazopyridines with N-Fluorobenzenesulfonimide. *The Journal of Organic Chemistry* **2018,** *83* (22), 13991-14000.

130. Meyet, C. E.; Pierce, C. J.; Larsen, C. H., A Single Cu(II) Catalyst for the Three-Component Coupling of Diverse Nitrogen Sources with Aldehydes and Alkynes. *Organic Letters* **2012,** *14* (4), 964-967.

131. Puratchikody, A.; Nagalakshmi, G.; Doble, M., Experimental and QSAR studies on antimicrobial activity of benzimidazole derivatives. *Chemical and Pharmaceutical Bulletin* **2008,** *56* (3), 273-281.

132. Garuti, L.; Roberti, M.; Rossi, T.; Cermelli, C.; Portolani, M.; Malagoli, M.; Castelli, M., Synthesis, antiviral and antiproliferative activity of some N-benzenesulphonyl-2-(2-or 3-pyridylethyl)-benzimidazoles. *Anti-cancer drug design* **1998,** *13* (5), 397-406.

133. Jin, H.; Xu, X.; Gao, J.; Zhong, J.; Wang, Y., Copper-Catalyzed One-Pot Synthesis of Substituted Benzimidazoles. *Advanced Synthesis & Catalysis* **2010,** *352* (2-3), 347-350.

134. Persson, A. K. Å.; Johnston, E. V.; Bäckvall, J.-E., Copper-Catalyzed N-Allenylation of Allylic Sulfonamides. *Organic Letters* **2009,** *11* (17), 3814-3817.

135. Cho, S. H.; Chang, S., Room Temperature Copper-Catalyzed 2-Functionalization of Pyrrole Rings by a Three-Component Coupling Reaction. *Angewandte Chemie International Edition* **2008,** *47* (15), 2836-2839.

136. Nagaraj, M.; Boominathan, M.; Perumal, D.; Muthusubramanian, S.; Bhuvanesh, N., Copper(I)-Catalyzed Cascade Sulfonimidate to Sulfonamide Rearrangement: Synthesis of Imidazo[1,2-a][1,4]diazepin-7(6H)-one. *The Journal of Organic Chemistry* **2012,** *77* (14), 6319-6326.

137. Bartholow, M., Top 200 drugs of 2011. *Pharmacy Times* **2012,** *78* (7).

138. DeBergh, J. R.; Niljianskul, N.; Buchwald, S. L., Synthesis of Aryl Sulfonamides via Palladium-Catalyzed Chlorosulfonylation of Arylboronic Acids. *Journal of the American Chemical Society* **2013,** *135* (29), 10638-10641.

139. Wang, X.; Xue, L.; Wang, Z., A Copper-Catalyzed Three-Component Reaction of Triethoxysilanes, Sulfur Dioxide, and Hydrazines. *Organic Letters* **2014,** *16* (15), 4056-4058.

140. Peng, J.; Xie, Z.; Chen, M.; Wang, J.; Zhu, Q., Copper-Catalyzed C(sp2)–H Amidation with Azides as Amino Sources. *Organic Letters* **2014,** *16* (18), 4702-4705.

141. Wang, X.; Yang, M.; Kuang, Y.; Liu, J.-B.; Fan, X.; Wu, J., Copper-catalyzed synthesis of sulfonamides from nitroarenes via the insertion of sulfur dioxide. *Chemical Communications* **2020,** *56* (23), 3437-3440.

142. Liu, Z.; Xiao, H.; Zhang, B.; Shen, H.; Zhu, L.; Li, C., Copper-Catalyzed Remote C(sp3)−H Trifluoromethylation of Carboxamides and Sulfonamides. *Angewandte Chemie International Edition* **2019,** *58* (8), 2510-2513.

143. Shi, S.; Zhang, P.; Luo, C.; Zhuo, S.; Zhang, Y.; Tang, G.; Zhao, Y., Copper-Catalyzed Remote C(sp3)–H Phosphorothiolation of Sulfonamides and Carboxamides in a Multicomponent Reaction. *Organic Letters* **2020,** *22* (5), 1760-1764.

144. Zhang, Y.; Yin, Z.; Wu, X.-F., Copper-Catalyzed Carbonylative Synthesis of β-Homoprolines from N-Fluoro-sulfonamides. *Organic Letters* **2020,** *22* (5), 1889-1893.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supportinginformation.docx