

# Cu/Fe-Catalyzed Carbon-Carbon and Carbon-Heteroatom Cross-Coupling Reactions

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## Abstract

Copper and iron salts are less toxic and inexpensive as compared to other transition metal salts. These salts have been extensively used for various carbon-carbon and carbon-heteroatom cross-coupling reactions. In this review, we described the Cu and Fe-mediated C-C, C-N, C-O, C-S and C-Se coupling reactions extensively. The synergistic effects of copper and iron salts towards the various bond-forming reactions have been presented. Use of such methods in the synthesis of bioactive molecules were also highlighted.

**Keywords:** Cu/Fe catalyst; Cross-coupling; Synergistic effect; Bioactive molecules

## Introduction

Recently, transition-metal (TM) catalyzed carbon-carbon and carbon-hetero bond forming reactions have received paramount attention because of their manifold industrial applications [1-6]. Historically, the metal-mediated C-C bond forming reaction was developed by Glaser [7] about 150 years back, which includes the oxidative dimerization of terminal acetylenes in the presence of stoichiometric amount of copper. At the beginning of 20<sup>th</sup> century (1901), Ullmann [8] discovered the copper-mediated synthesis of biaryls from the coupling of activated aryl bromides. Later, the scope of this method has been extended to carbon-hetero bond forming reactions in the presence of stoichiometric amounts of copper salt at high reaction temperature. The synthesis of acetaldehydes by palladium-catalyzed Wacker oxidation of ethylene, discovered in 1956, probably is the first Pd-catalyzed reaction [9] that revolutionized the chemical synthesis. Then after, numerous carbon-carbon and carbon-hetero coupling reactions were developed. Undoubtedly, these coupling reactions boost a new direction for the synthesis of complex molecules from simple molecules with the aid of transition metals. In spite of having wide scope and excellent compatibility with many functional groups, these protocols, often suffer from the limitations resulting from (i) the high cost of the palladium precursors, (ii) the need for ancillary ligands rendering the catalysts sufficiently reactive, (iii) concerns about the toxicity of these metal salts, and (iv) the extended reaction time necessary in many cases. Considering the cost and environmental factors, the use of Cu- and Fe-based catalysts for various coupling reactions is more attractive from industrial perspectives [10-13]. Indeed, copper-mediated synthesis of diarylacetylenes from the cross-coupling aryl acetylene and aryl halides at relatively lower temperature (under refluxing pyridine) was well reported earlier by Castro and Stephens [14]. Later, Sonogashira observed that the coupling between terminal alkynes with aryl halides in the presence of catalytic amount of palladium and copper [15]. Buchwald and Taillefer also independently made a significant breakthrough on Cu-catalyzed cross-coupling reactions by introducing chelating ligands [16-18]. Use of ligands in such processes not only accelerates the rate of coupling reaction, but also softens the reaction conditions aiming to widen the substrate scope. In this review a systematic progress of copper/iron-catalyzed carbon-carbon and carbon-hetero (C-N, C-O, C-S and C-Se) cross-coupling reactions, and synthesis of bioactive molecules using these techniques have been presented.

## C-C cross-coupling Reactions

During the last five decades, dramatic progress has been made on transition-metal-catalyzed C-C bond forming reactions. Numerous research groups stretch their research objective towards the development of new catalytic systems with wide substrate scope under mild reaction conditions. As a result of which vast number of methodologies for several types of C-C bonds (*viz*, C(sp)-C(sp), C(sp<sup>2</sup>)-C(sp<sup>2</sup>), C(sp)-C(sp<sup>2</sup>), C(sp<sup>3</sup>)-C(sp<sup>3</sup>), C(sp<sup>2</sup>)-C(sp<sup>3</sup>)) forming reactions have been explored [19-21].

### C(sp)-C(sp) bond formations

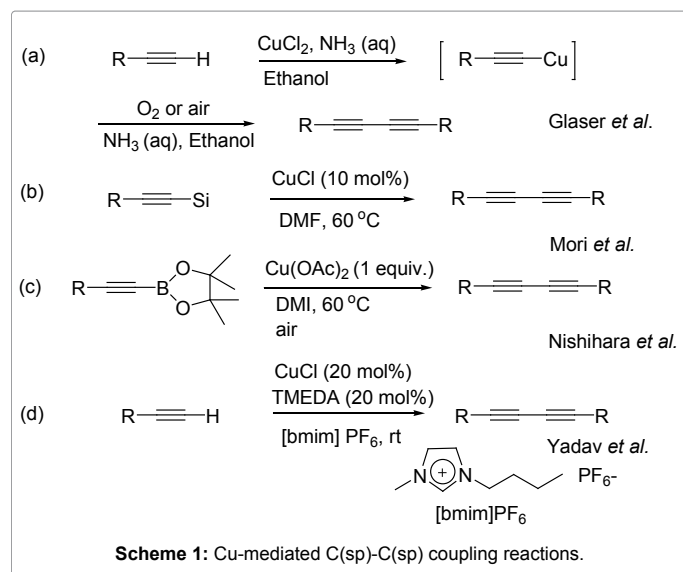
The copper promoted acetylenic coupling is found its application in the synthesis of natural products as well as functional materials [22-23]. Glaser, in 1869 first reported the copper-mediated dimerization of terminal alkynes to generate diacetylenes through the C(sp)-C(sp) bond forming reaction. In this reaction, stoichiometric amount of copper salt was expended to form copper acetylene intermediate, which subsequently oxidized in the presence of air or O<sub>2</sub> to give symmetrical diyne (Scheme 1a) [7]. The advantages of this C(sp)-C(sp) bond forming reaction was adopted by the synthetic community during the following decades by exploring a number of synthetic variations to the Glaser coupling. These variants differ from the original coupling reaction with respect to the oxidants, substrates and the amount of copper catalyst. For instance, Hay dimerized the terminal alkynes at room temperature by using catalytic amount of CuCl in pyridine [24]. Terminally silicon substituted alkynes, such as alkynyl silanes were also employed for Glaser homocoupling reactions by Mori et al. using catalytic amount of CuCl in DMF (Scheme 1b) [25]. Later, Nishihara reported [26] the similar homocoupling reactions by choosing alkynylboronates as coupling partner in the presence of stoichiometric amount of copper acetate (Scheme 1c). Yadav et al. [27] made an

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improvement by conducting the ligand-assisted copper-catalyzed dimerization of terminal alkynes in the presence of ionic liquid (e.g. [bmim]PF<sub>6</sub>) (Scheme 1d).

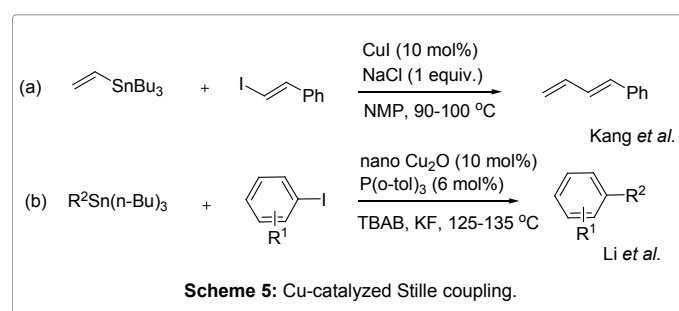
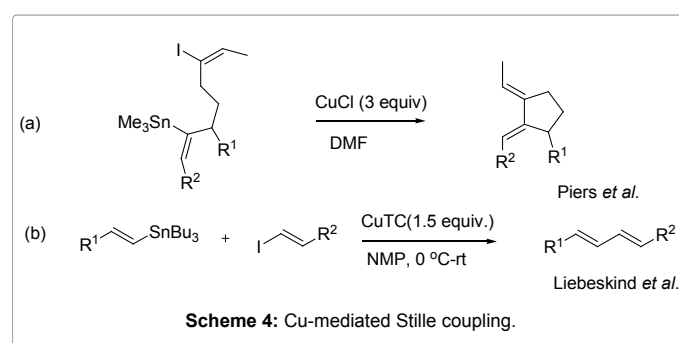
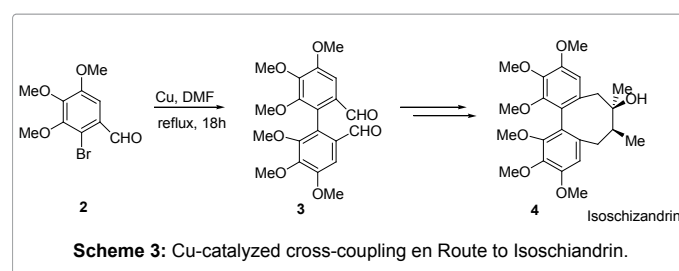
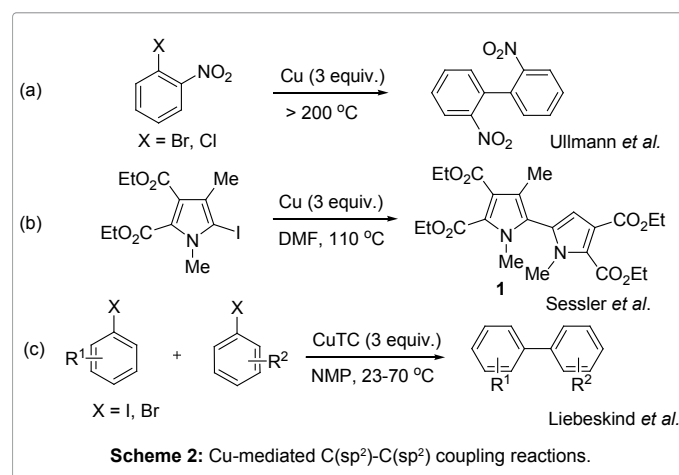
### C(sp<sup>2</sup>)-C(sp<sup>2</sup>) bond formations

Following the conceptual development on C(sp)-C(sp) homocoupling reaction by Glaser, similar Cu-mediated method was adopted by Ullmann in 1901, for the construction of C(sp<sup>2</sup>)-C(sp<sup>2</sup>) bond between aryl halides [8]. He reported the dimerization of 2-bromo- and 2-chloronitrobenzene in the presence of super stoichiometric amount of copper sources at high temperature (≈220°C) (Scheme 2a). In spite of the harsh reaction conditions and requirement of excess copper salt, Ullmann reaction was followed by the organic community for a long time to achieve biaryls. Since last six decades, numerous efforts have been made to extend the substrate scope as well as to soften the reaction conditions intending to the formation of less amount of waste by converting the coupling process to a catalytic one. A modified methodology [28] which includes the use of DMF as solvent, permits the coupling reaction to occur at lower temperature. Sessler et al. [29] utilized activated Cu(0) obtained from the reduction of CuI with potassium, for the synthesis of substituted 2,2'-bipyrrrole **1** at relatively lower temperature (110°C) (Scheme 2b). Further decrease in temperature was observed by Liebeskind et al. [30] by applying copper(I)-thiophene-2-carboxylate (CuTC) in NMP (Scheme 2c). The modified Ullmann coupling reactions were found applications in total synthesis of natural and non-natural products. For instance, **3**, an intermediate for (+)-isochizandrin **4**, was readily accessed by the copper-mediated Ullmann coupling of the corresponding haloaldehyde **2** (Scheme 3) [31].

Copper-mediated intramolecular coupling of vinyl tin derivatives with vinyl iodide leading to conjugated diens through C(sp<sup>2</sup>)-C(sp<sup>2</sup>) bond formation was reported by Piers et al. (Scheme 4a). This reaction might be a Cu-catalyzed analogue of Stille coupling reaction [32]. Intermolecular coupling of organostannanes with the aryl, heteroaryl and vinyl iodides to furnish 1,3-dienes in the presence of stoichiometric amount of copper(I)-thiophene carboxylate (CuTC) was also reported (Scheme 4b) [33].

Furthermore, the copper-promoted catalytic version of the former coupling reaction was developed by Kang et al. [34]. They described the

cross-coupling between organostannanes with aryl iodides employing catalytic amount of CuI in NMP (Scheme 5a) albeit stoichiometric amount of sodium chloride is needed to obtain the optimum yield of conjugated alkene. Li et al. [35] developed the ligand-assisted Cu<sub>2</sub>O nanoparticles-mediated coupling of aryl halides with organotin derivatives in the presence of TBAB. This nanocatalyst was reported to be recyclable up to five consecutive runs for aryl iodides and activated aryl bromides. However, in case of deactivated aryl bromides the efficiency of the catalyst was limited to single run only (Scheme 5b).



Copper-catalyzed cross-coupling between organotin derivatives with vinyl iodide has been exploited for the total synthesis of complex natural products. For example, Peterson et al. [36] performed the total synthesis of Concanamycin **8** in which the intermediate **7** was prepared by the copper-mediated coupling between vinyl iodide derivatives **5** and vinyl stannane derivatives **6** (Scheme 6). The cross-coupling of arylboronic acid with aryl and vinyl halides has been emerged as a potential method for the formation of C(sp<sup>2</sup>)-C(sp<sup>2</sup>) bond. This method has several advantages including the use of commercially available starting materials, generation of non-toxic by-products, negligible steric consideration and wide functional group tolerance. In 1996, Kang et al. [37] reported the CuI catalyzed coupling between boronic acid derivatives and iodonium salts in aqueous DME to access biaryls (Scheme 7).

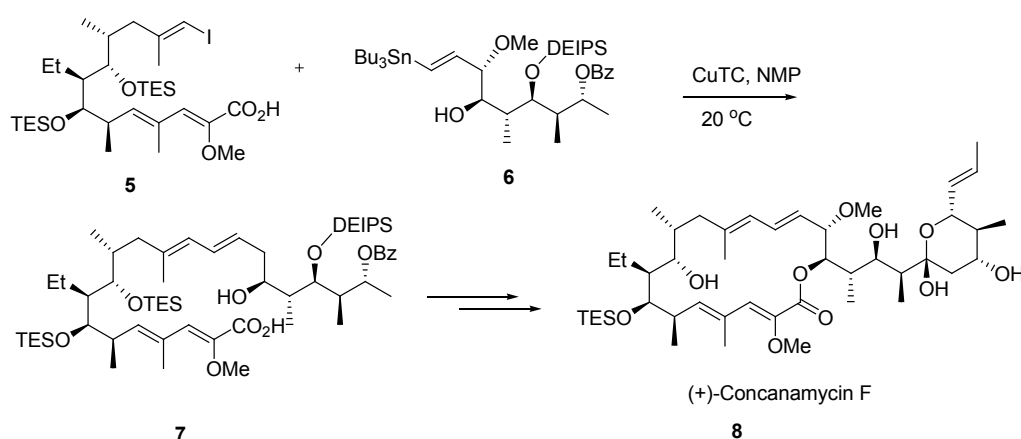
Later, the ligand-assisted copper-catalyzed coupling between arylboronic acids with vinyl halides and aryl halides to form C(sp<sup>2</sup>)-C(sp<sup>2</sup>) bond was also developed (Scheme 8). Li et al. [38] found that CuI-catalyzes the coupling of aryl boronic acid with vinyl halides or aryl halides the presence of TBAB to afford diarylethenes and biaryls respectively in moderate to good yield.

The copper-catalyzed coupling of aryl and vinyl halides with the

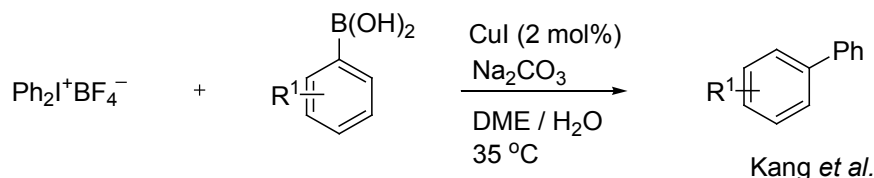
olefins to form C(sp<sup>2</sup>)-C(sp<sup>2</sup>) bond was also precedent in literature. In 1997, Iyer reported the synthesis of aryl-alkenes and conjugated alkenes by coupling between olefins with aryl and vinyl iodides using stoichiometric amount of copper iodide in *N*-methylpyrrolidone (NMP) (Scheme 9) [39]. Use of DABCO as a ligand in such coupling reaction was also reported [40].

Besides, the significant developments on copper-based homogeneous catalytic systems for C(sp<sup>2</sup>)-C(sp<sup>2</sup>) coupling reactions, the use of heterogeneous catalytic system also found to be interesting. Mao et al. [41] applied the readily available copper powder for the coupling between aryl iodides with boronic acids in PEG-400. Using iodine as additive, the coupling between aryl bromides and chlorides with boronic acids was found to be successful. Rothenberg et al. [42] applied the copper nanocluster for the coupling between aryl halides and arylboronic acids (Scheme 10). Di- and trimetallic clusters showed enhanced reactivity in the coupling of arylboronic acids with activated aryl bromides and aryl chlorides.

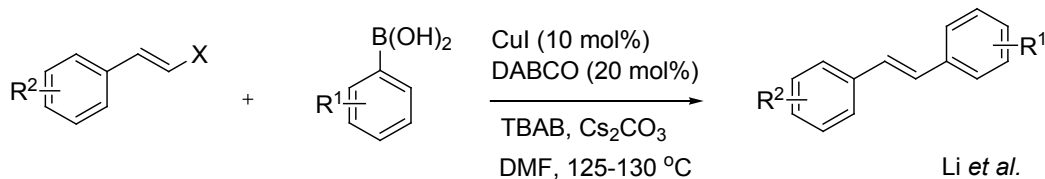
With emerge of nanotechnology; copper nanoparticles were also employed for the coupling of aryl iodides and butyl acrylates [43]. In such cases copper nanoparticles were produced in-situ by reduction of copper bronze and promoted the Heck coupling reaction to produce the internal alkene (Scheme 11).



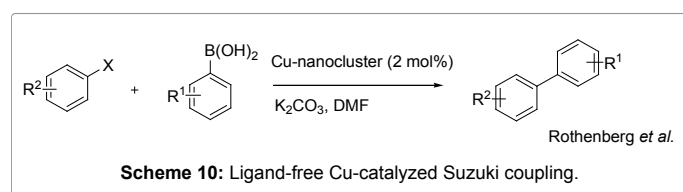
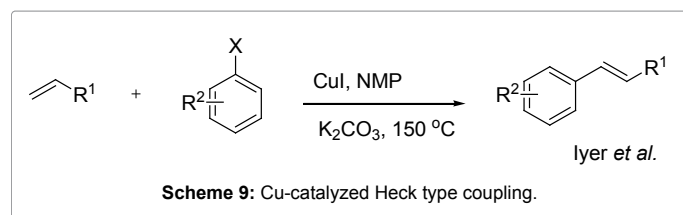
Scheme 6: Cu-catalyzed Stille coupling en Route to (+)-Concanamycin F.



Scheme 7: Cu-catalyzed Suzuki coupling.



Scheme 8: Ligand-assisted Cu-catalyzed Suzuki coupling.



Owing to the wide abundance and low cost, iron catalysts were successfully employed for C(sp<sup>2</sup>)-C(sp<sup>2</sup>) bond forming reactions. Iron catalyzed homocoupling of aryl Grignard reagent was first reported by Kharasch and Field in 1941 to produce symmetrical biaryls (Scheme 12a) [44]. Subsequently a series of C-C bond forming reactions were also developed. Notably, the scope of Fe-catalyzed C(sp<sup>2</sup>)-C(sp<sup>2</sup>) bond forming reactions was expanded by Cahiez *et al.* [45,46] in the beginning of 21<sup>st</sup> century to produce wide varieties of substituted biaryls (Scheme 12b).

Nakamura *et al.* [47] also exploited the catalytic efficiency of Fe-catalyst in cross-coupling reaction to produce unsymmetrical biaryls in good yield (Scheme 13). Notably, homocoupling of the Grignard reagent is effectively reduced when FeF<sub>3</sub> is employed in combination with an *N*-heterocyclic carbene ligand. The specific effect of fluoride was demonstrated by the addition of KF to FeCl<sub>3</sub> catalyst precursor, which otherwise provides predominately homocoupling product. Vogel *et al.* [48] reported the iron-catalyzed coupling of styrenes with aromatic and heteroaromatic iodides using picolinic acid as chelating agent and potassium *tert*-butoxide as base.

In an interesting report [49], synthetic potential of iron/copper cooperative catalyst was illustrated by the preparation of 17-arylstrene derivatives (Figure 1) related to abiraterone acetate (Zytiga, CYP17 inhibitor), a new drug currently used in the treatment of metastatic prostate cancer [50].

### C(sp)-C(sp<sup>2</sup>) bond formations

The coupling between alkynes with aryl or vinyl halides resulted the formation of C(sp)-C(sp<sup>2</sup>) bond. In 1993, Miura *et al.* reported ligand-assisted copper-catalyzed synthesis of aryl-alkynes and vinyl-alkynes by coupling terminal alkynes with aryl halides and vinyl halides respectively (Scheme 14) [51]. Under similar catalytic conditions, Li *et al.* prepared the aryl-alkynes in the presence of DABCO which act as a chelating ligand [38].

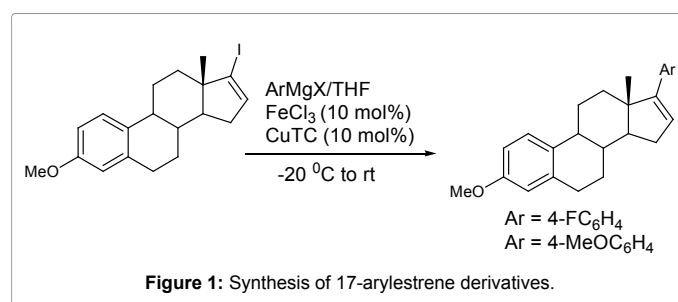
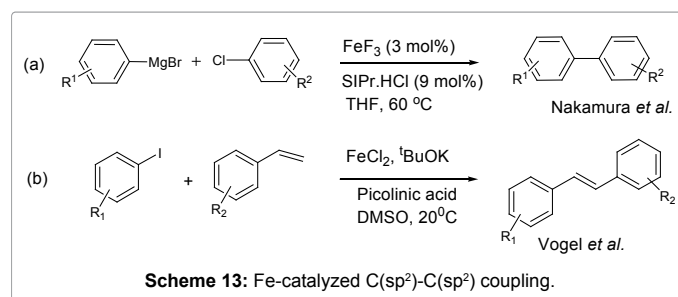
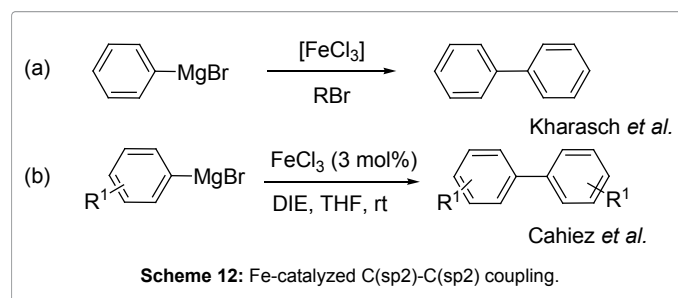
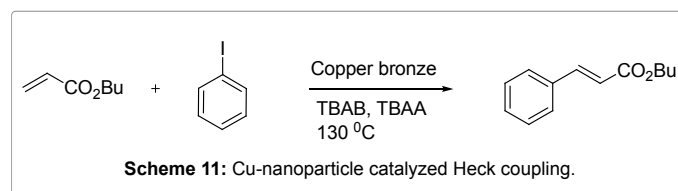
Later, Venkataraman *et al.* [52] observed that if the solubility of the copper salts would be increased, the reaction would occur under mild reaction conditions. Thus, they prepared a soluble copper complex (C1) and conducted the C(sp)-C(sp<sup>2</sup>) coupling between phenyl acetylenes and aryl iodides in toluene at its boiling point (Scheme 15).

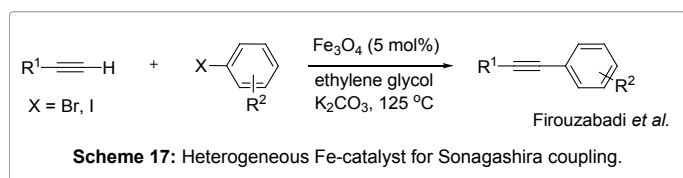
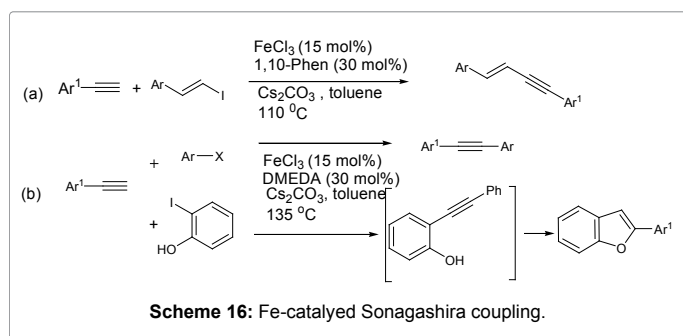
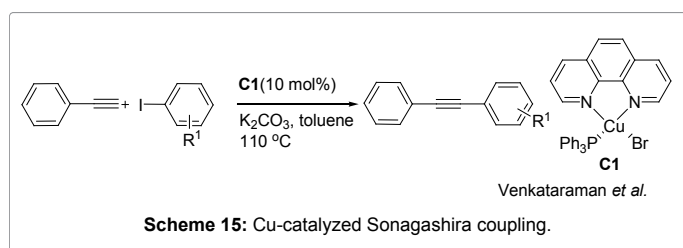
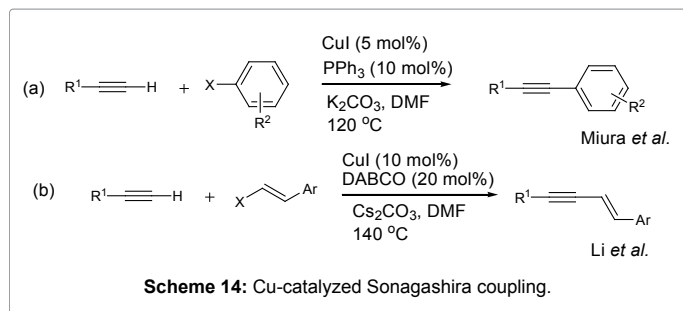
Although copper-catalyzed sp-sp<sup>2</sup> coupling reactions were well reported, the development of iron-catalyzed C-C coupling reactions was also encouraging, owing to the cheap and environmental friendly nature of iron. In this regard, coupling of terminal alkynes with alkenyl iodides in the presence of FeCl<sub>3</sub> and 1,10-phenanthroline (Scheme

16a) was reported [53]. Use of other ligands such as DMEDA and 2,2'-bipyridine was also found to be effective for the coupling aryl and heteroaryl iodides with terminal alkynes to form C(sp)-C(sp<sup>2</sup>) bond [54,55]. An iron catalyzed sonogashira coupling followed by cyclization produces the 2-arylbenzofuran (Scheme 16b).

Recently heterogeneous, recyclable Fe<sub>3</sub>O<sub>4</sub> nanoparticles-mediated coupling between terminal alkynes with aryl and heteroaryl halides in ethylene glycol were reported by Firouzabadi *et al.* (Scheme 17) [56].

Although these Fe-catalyzed C-C bond forming reactions are interesting, but it is limited to long reaction time (e.g. 72 h) and narrower substrate scope. For example, FeCl<sub>3</sub>/DMEDA condition reported by Bolm [54] was unsuccessful with aliphatic terminal alkynes. In order to expand the substrate scope and efficiency, development of more sustainable catalytic system is promising. The use of cheap and environmental benign iron salts in combination with copper would be noteworthy. In this line, Liu *et al.* [57] described a ligand-assisted Cu-Fe co-catalytic method for the C(sp)-C(sp<sup>2</sup>) coupling reactions. They found that Fe<sub>2</sub>O<sub>3</sub> in combination with Cu(acac)<sub>2</sub> was suitable for





the cross-coupling between terminal alkynes with aryl and heteroaryl halides using TMEDA as the ligand (Scheme 18a). Later, Vogel et al. [58] reported Cu/Fe(acac)<sub>3</sub> catalyzed arylation of both terminal alkyne and aryl alkynes at 140°C in NMP (Scheme 18b). In this context we have also developed magnetic copper ferrite nanoparticle-mediated cross-coupling reactions between terminal alkynes with aryl halides (Scheme 18c) [59]. Magnetic nature of the catalyst helps to recover the catalyst quantitatively and reused for three consecutive cycles without any range in catalytic activity.

### C(sp<sup>2</sup>)-C(sp<sup>3</sup>) bond formations

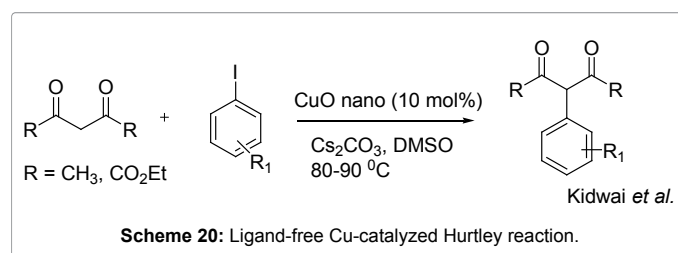
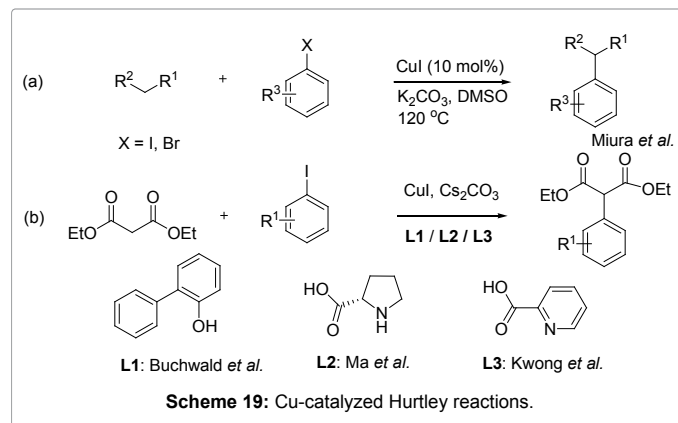
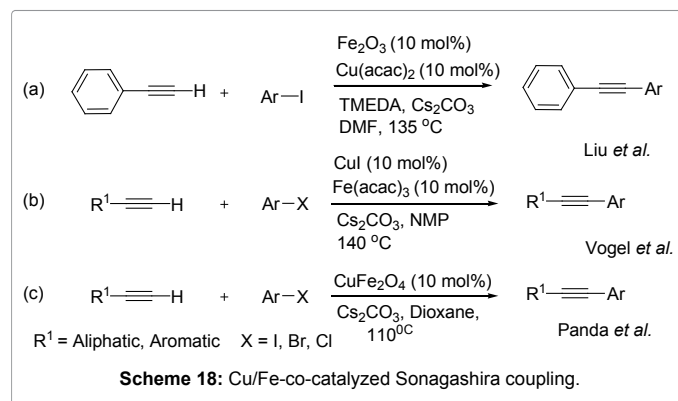
The first example on copper-mediated coupling of the 1,3-dicarbonyl compounds with 2-bromobenzoic acid in the presence of strong base (*ca* KOH) at 160°C was reported by Hurtly in 1929 [60]. This reaction proceeds through the copper-carboxylate intermediate, that polarized the C-X bond, which subsequently attacked by the carbanion of 1,3-dicarbonyl compound to form the C(sp<sup>2</sup>)-C(sp<sup>3</sup>) bond. Later, extensive efforts have been made to soften reaction conditions. For instance, Miura et al. [61] reported a copper-mediated sp<sup>2</sup>-sp<sup>3</sup> coupling between active methylene compounds and aryl iodides

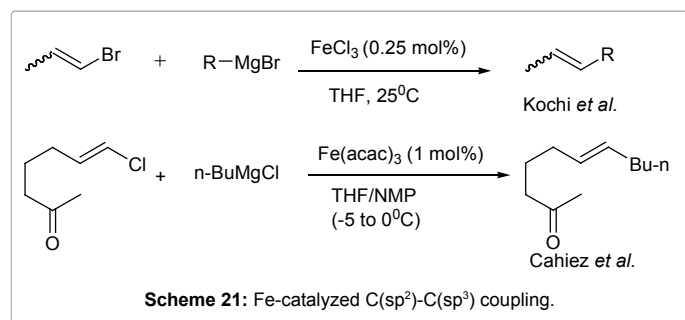
in the presence of K<sub>2</sub>CO<sub>3</sub> in DMSO at 120°C (Scheme 19a). Then, ligand-assisted copper-promoted coupling reactions were developed which requires lower temperature (Scheme 19b). Evidently, Buchwald et al. [62] reported that 2-phenylphenol L1 which acts as an efficient ligand for the coupling 1,3-dicarbonyl compounds with aryl iodide at 70°C in THF. Subsequently, other ligands such as L-proline L2 [63] and 2-picolinic acid L3 [64] were employed to promote such coupling reaction between 1,3-diketones with aryl iodides and bromides.

Heterogeneous copper nanoparticles were also employed for C(sp<sup>2</sup>)-C(sp<sup>3</sup>) coupling reactions aiming to the reusability of the catalyst. For instance, Kidwai et al. reported the recyclable CuO nanoparticle-mediated coupling between 1,3-diketones with aryl iodides in DMSO (Scheme 20) [65].

Besides, iron-catalyzed such coupling reactions were also well reported. For example, in 1971, Kochi [66] first exploited the iron catalyst (e.g. FeCl<sub>3</sub>) for the cross-coupling between organomagnesium reagents with alkynyl bromides (Scheme 21). Cahiez and Avedissian found that an excess amount of NMP is beneficial for iron-catalyzed cross-coupling of alkenyl halides with alkyl magnesium reagents [67].

Fürstner et al. [68,69] observed that the iron-catalyzed cross-





coupling reactions proceed most efficiently with chloride substrates, which is in contrast to the aryl iodides or bromides usually required for palladium cross-coupling reactions (Scheme 22a,b). Interestingly, Grignard reagents undergo cross-coupling faster than they react with other electrophilic sites in the substrate. For example, ketones, aldehydes, esters, ethers, nitriles, and even trimethylsilyl groups in the electrophilic halide partner are unaffected under such iron-catalyzed cross-coupling conditions. Nakamura et al. [70] have shown that iron catalysts are capable of inserting into both primary and secondary sp<sup>3</sup>-hybridized carbon-halide bonds to affect cross-coupling (Scheme 22b). A mild protocol for the stereoselective sp<sup>2</sup>-sp<sup>3</sup> couplings were also demonstrated by Cahiez et al. [71]. They used similar catalyst in the presence of chelating ligands, like TMEDA and HMTA for the coupling of vinyl Grignard with alkyl halides (Scheme 22c). Fürstner et al. [72] also exploited the high reactivity of iron catalyst in the coupling of alkenyl electrophiles with organomagnesium reagents without affecting the ester group and alkynes. This reaction has been employed as a key step in the synthesis of latrunculin B (Scheme 22d). Other natural products such as muscopyridine [73], cubene, ambhidinolide Y, etc. were also synthesized using Fe-catalyzed coupling reaction as a key reaction (Figure 2).

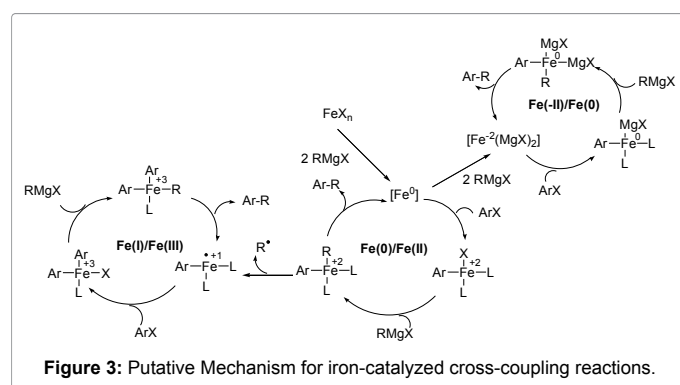
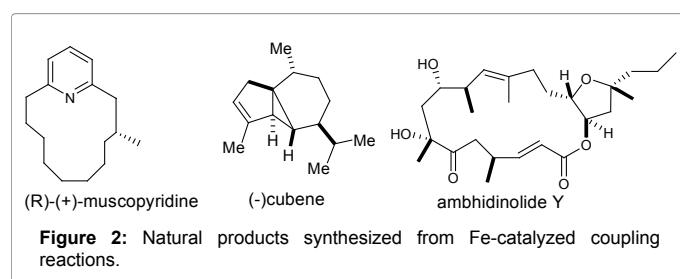
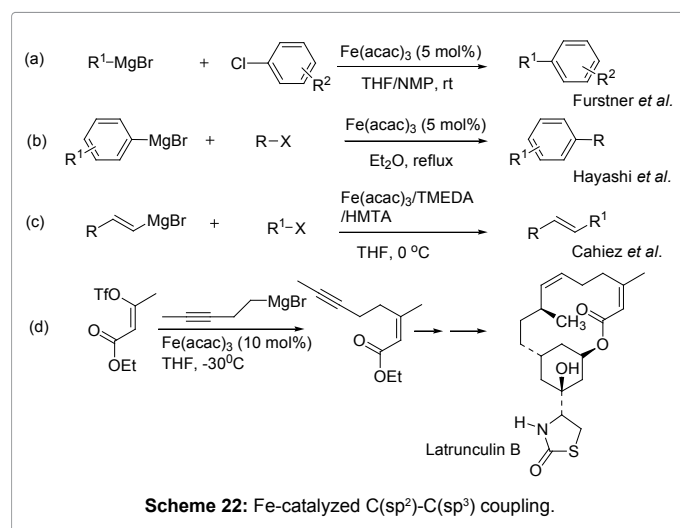
Early studies on the coupling of alkyl and alkenyl bromides with alkylmagnesium reagents by Kochi [66] comprise the involvement of Fe(I) and Fe(III) species through a sequence of oxidative addition, transmetalation, and final reductive elimination step. Although Fe(I) was depicted as the active species in the original paper, the equivalent process involving Fe(0) was considered equally feasible (Figure 3) [66]. The active component in this reaction is metastable and loses its catalytic efficiency rapidly in the absence of substrate. Studies on similar coupling reaction of Grignard reagents containing β-hydrogens with halides in the presence of stoichiometric amount of FeCl<sub>2</sub> suggest that an overall four-electron reduction of iron salt by Grignard reagent takes place, leading to a bimetallic species with formal constitution [Fe(MgCl)<sub>2</sub>]<sub>n</sub>, which likely consists of small clusters incorporating magnesium and iron centres that are connected via fairly covalent intermetallic bonds [74]. The catalytic cycle expected to involve the typical sequence of oxidative addition, transmetalation, and reductive elimination steps (although the catalyst alternates between the 0 and -2 oxidation states). Reactions employing radical probes and labeled substrates also suggest the involvement of radicals in iron-catalyzed cross-coupling reactions [75]. Radicals may be generated from Fe(II) complexes that “cross-over” into the Fe(I)/Fe(III) catalytic cycle via homolytic cleavage of an iron-carbon bond. Possible involvement of different oxidation states of iron to catalyze the cross-coupling is presented below (see Figure 3).

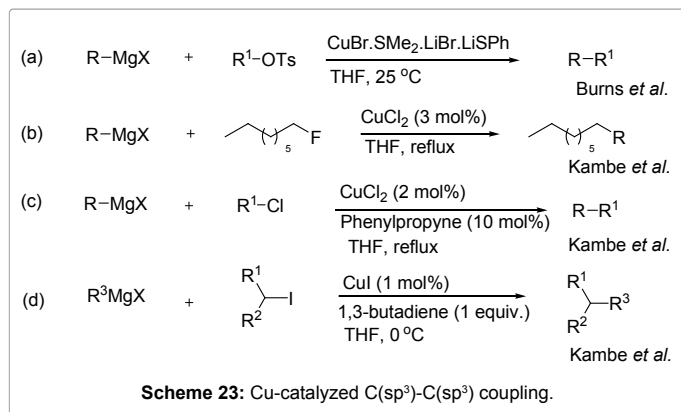
### C(sp<sup>3</sup>)-C(sp<sup>3</sup>) bond formations

The C(sp<sup>3</sup>)-C(sp<sup>3</sup>) coupling reactions between alkyl derivatives were less reported as compared to other types of C-C coupling reactions

discussed earlier. This may be due to the alkyl metal intermediate generated in situ in the catalytic cycle undergoes β-hydride elimination reaction. Moreover, this intermediate also participates in other undesired reactions [76-79]. In 1997, Burns et al. reported a copper-catalyzed sp<sup>3</sup>-sp<sup>3</sup> coupling reaction between alkyl Grignard reagents with alkyl pseudohalides (Scheme 23a) [80]. Later, Kambe et al. [81-83] reported the Cu(II)-catalyzed coupling between octyl fluorides and alkyl Grignard reagents (Scheme 23b). The same group further also used 1-phenylpropyne [82] and 1,3-butadiene [83] separately as additives to broaden the substrate scope of the sp<sup>3</sup>-sp<sup>3</sup> bond forming reaction (Scheme 23c,d).

Recently, copper-mediated C(sp<sup>3</sup>)-C(sp<sup>3</sup>) cross-coupling between non-activated secondary alkyl halides and pseudo halides with secondary Grignard reagents were reported by Liu et al. [84]. They explored the C-C bond formation by using CuI as catalyst and TMEDA as additive (Scheme 24).





## C-N Cross-Coupling Reactions

TM-mediated C-N cross-coupling reactions constitute a powerful strategy for the synthesis of numerous fine chemicals as well as compounds of biological importance [85]. Since 1903, copper catalyzed Ullmann cross-coupling is used traditionally for the C-N bond forming reactions [8]. The classic Ullmann reaction normally requires harsh conditions, such as high temperature (200 °C), stoichiometric amounts of copper and selective halide substrates, which is problematic for large scale use due to high cost and waste disposal. In order to circumvent such limitations considerable efforts have been made focusing on the development of cheap, eco-friendly catalytic systems under mild reaction conditions. In this regard, we wish to present the significant developments on Cu/Fe-catalyzed C-N cross-coupling reactions [10-13]. Gratifyingly, after about 95 years of Ullmann C-N cross-coupling reaction, Chan et al. [86] and Lam et al. [87] independently illustrated the copper-catalyzed coupling of arylboronic acids with amines and NH-heterocycles (Scheme 25). However, the high cost and relative instability of boronic acids, and tedious purification procedure often limit their extensive application in laboratory as well as industrial scale.

Subsequently, Buchwald [88] and Hartwig [89] were independently employed palladium-based catalysts for the *N*-arylation of amines with aryl halides. However, toxicity and high cost of Pd catalysts are the obvious limitations associated with this method for large scale implementation. Thus, researchers have turned their attention toward the use of less expensive, less toxic and more efficient metals to replace Pd [10-13, 90,91]. Indeed, Buchwald [92] and Taillefer [93] independently made a significant breakthrough in the copper-catalyzed cross-coupling of NH-heterocycles with aryl halides in the presence of chelating ligands (Scheme 26).

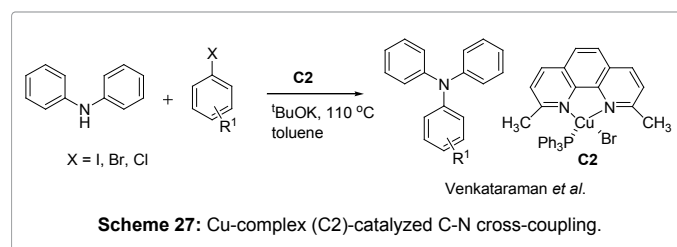
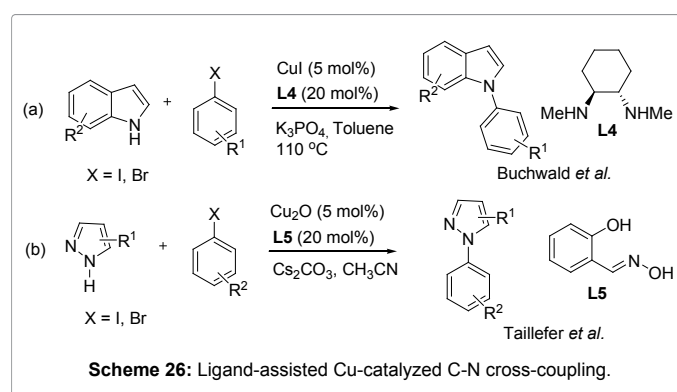
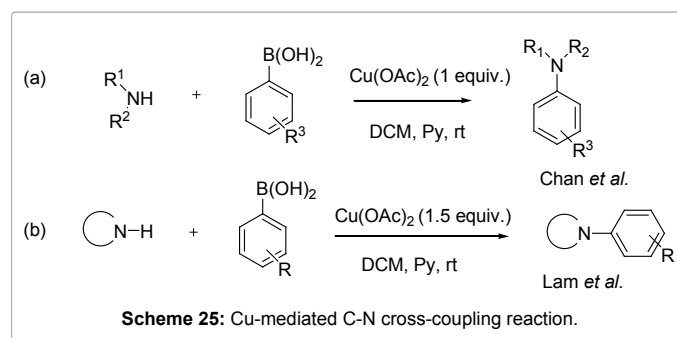
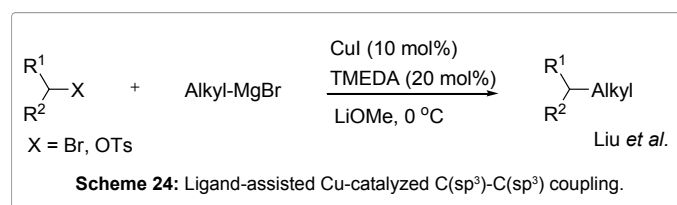
In due time, numerous *N*, *O*-containing ligands such as *L*-proline, *N*-methylglycine, *N,N'*-dimethylcyclohexane-1,2-diamine, DPP, 1,3-diketone, 4,7-dimethoxy-1,10-phen., 8-hydroxyquinoline, 2-aminopyrimidine-4,6-diol, *rac*-BINOL, 4,7-dimethoxy-1,10-phenanthroline, ninhydrin, picolinic acid etc. were employed by various researchers for the copper-mediated C-N coupling reactions [10-13,90,91].

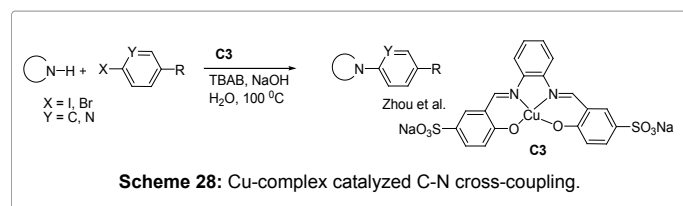
Venkataraman et al. [52] prepared a soluble copper catalyst (C2) for the cross-coupling of diarylamines with aryl halides. They found that 10 mol% of the catalyst is sufficient in coupling of the diaryl amines with the aryl halides including the less reactive chlorobenzene in toluene at 110 °C (Scheme 27).

Bao et al. [94] reported CuI/*L*-Proline catalytic systems for coupling

the imidazoles with aryl and heteroaryl bromides in ionic liquids [Bmim]BF<sub>4</sub>. They found that 30 mol% of CuI with 60 mol% of *L*-Proline was effective for the coupling of imidazoles and benzimidazoles with aryl and heteroaryl bromides in the presence of [Bmim]BF<sub>4</sub> (1 ml/mol). Interestingly, the catalytic system, CuI/*L*-Proline/[Bmim]BF<sub>4</sub>, found to be recyclable and reusable up to four consecutive runs. Zhou et al. [95] described the *N*-arylation of imidazoles and indoles with aryl bromides and iodides using the copper complex C3 in aqueous medium (Scheme 28).

On the other hand, the simple separation and regeneration of the catalyst from the reaction mixture are in strong demand for the cost-effective process of molecular synthesis. Thus, ligand-free cross-coupling reactions attracted wide attention. The earliest contributions were made by Taillefer et al. [96]. They performed the coupling between iodo- and bromobenzene with nitrogen heterocycles using catalytic quantity of CuI in CH<sub>3</sub>CN (Scheme 29a). Later, Bolm et al.





[97] proposed Cu<sub>2</sub>O-mediated C-N coupling between azoles with aryl iodides and bromides in DMF under ligand-free conditions (Scheme 29b). Same group also reported that the amination of halopyridines with nitrogen nucleophiles occurred under solvent and ligand-free conditions in the presence of microwave irradiation (Scheme 29c) [98]. Very recently, Fu et al. developed an efficient photo-induced protocol for C-N cross-coupling reaction at room temperature (Scheme 29d). The methodology was successful for coupling the NH-heterocycles with a wide range of arylhalides, heteroaryl halides and alkynyl halides in the presence of catalytic amount of CuI [99]. The reaction proceeds through the initial photo-excitation of the copper-azole complex followed by the electron transfer reactions with aryl halides, affording the N-arylated product in good yield.

Numerous heterogeneous catalysts were also employed for the C-N cross-coupling reactions aiming to the simple purification and reusability of the catalyst. One of the interesting examples was reported by Choudary et al, [100] in which the supported copper fluoroapatite (CuFAP) was used for the N-arylation of N-containing heterocycles even with less reactive aryl chlorides and aryl fluorides (Scheme 30).

Kantam et al. [101] demonstrated a ligand-free, reusable cellulose-supported Cu(0)-catalyzed N-arylation of NH-heterocycles with aryl bromides and iodides in DMSO (Scheme 31).

Copper (I) oxide in PEG support were also efficiently used as a recyclable catalyst for the C-N cross-coupling reactions. Lamaty et al. [102] reported microwave assisted Cu<sub>2</sub>O-PEG for the coupling between benzimidazoles and indoles with aryl halides (Scheme 32).

Recently, Wan et al. [103] reported CuI/PSP (Polystyrene-supported pyrrole-2-carbohydrazide) catalytic system for the C-N coupling between amines with aryl halides in aqueous medium (Scheme 33). They applied the methodology towards the synthesis of imidazo[1,2-a]quinoxaline.

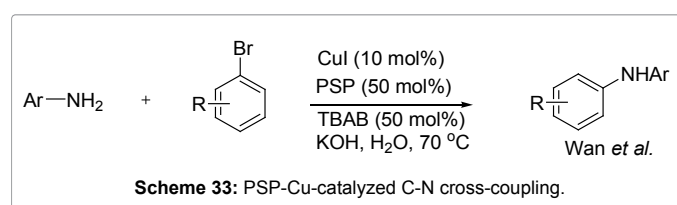
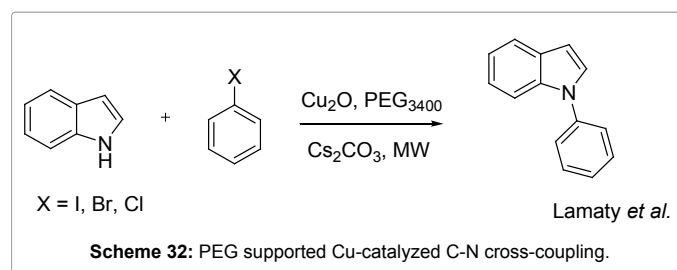
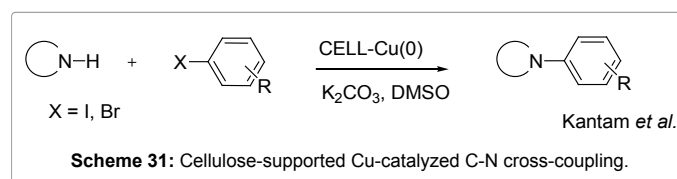
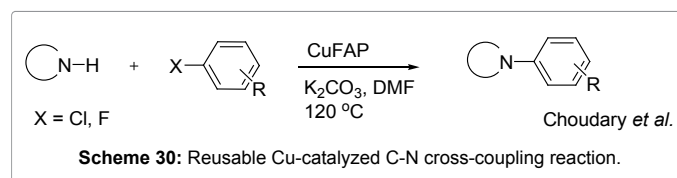
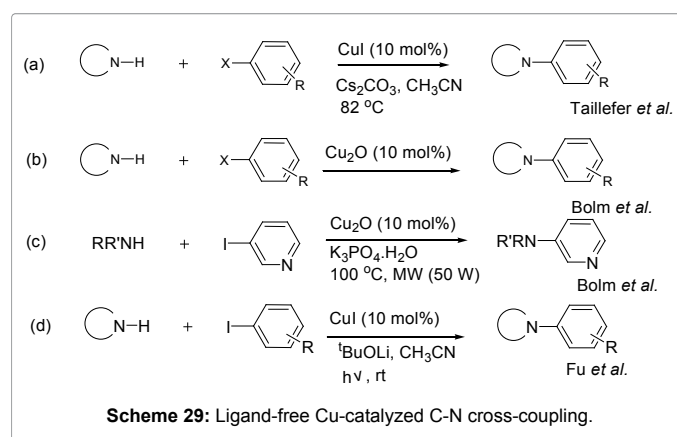
Reusable copper nanoparticles were also utilized for the C-N cross-coupling reactions exploiting the high surface area and low coordination sites of the catalyst. Evidently, Hyeon et al. [104] used Cu<sub>2</sub>O-coated Cu nanoparticles for the coupling between nitrogen nucleophiles with activated aryl chlorides (Scheme 34a). Later, CuO nanoparticles were successfully employed by Punniamurthy et al. [105] for the N-arylation of various N-containing precursors (Scheme 34b). Kantam et al. [106] were also exploited the high surface area and reactive morphology of the CuO nanoparticles for the C-N cross-coupling reactions between NH-heterocycles with aryl chlorides and aryl fluorides (Scheme 34c).

In parallel to Cu-catalyzed C-N cross-coupling reactions, the Fe-catalyzed reactions were also explored. The pioneering efforts on Fe-catalyzed C-N coupling reactions were made by the Bolm [97]. They showed the potential of FeCl<sub>3</sub> in presence of DMEDA for the N-arylation of NH-heterocycles with differently substituted aryl iodides and bromides in refluxing toluene (Scheme 35).

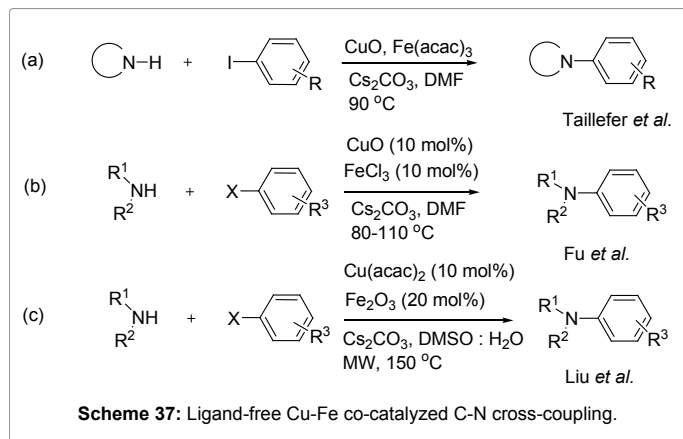
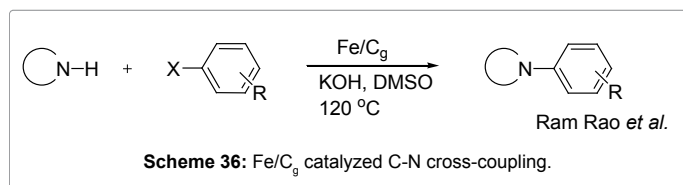
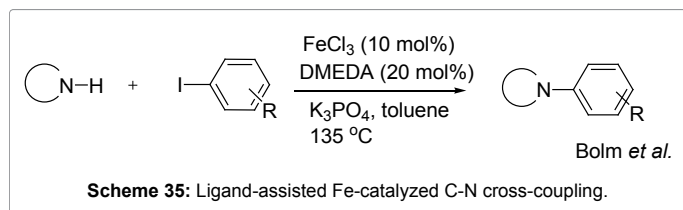
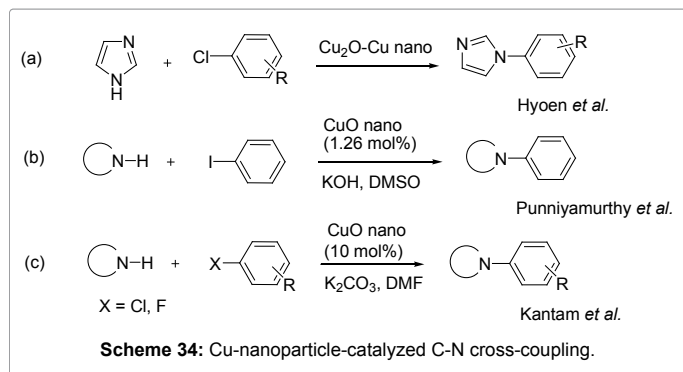
Later, Rama Rao [107] prepared recyclable graphite supported iron

catalyst and applied for the coupling between nitrogen heterocycles with aryl halides under ligand-free conditions (Scheme 36).

The Cu-Fe co-operative catalysts were also developed for the C-N cross-coupling reactions to extend the scope as well as to improve the yield. In 2006, Taillefer et al. [108] illustrated the first example on Cu/Fe co-catalyzed protocol for the N-arylation reaction of various nitrogen heterocycles with aryl halides including the less reactive activated aryl chlorides in DMF (Scheme 37a). It may be noted that neither Fe(acac)<sub>3</sub> nor CuO alone are suitable for the N-arylation of pyrrole. However, Cu/Fe-cooperated catalyst leads to the N-arylated heterocycles in good to excellent yield without affording by-products resulting from biaryl coupling or from the reduction of aryl halides [108]. In line this Fu et





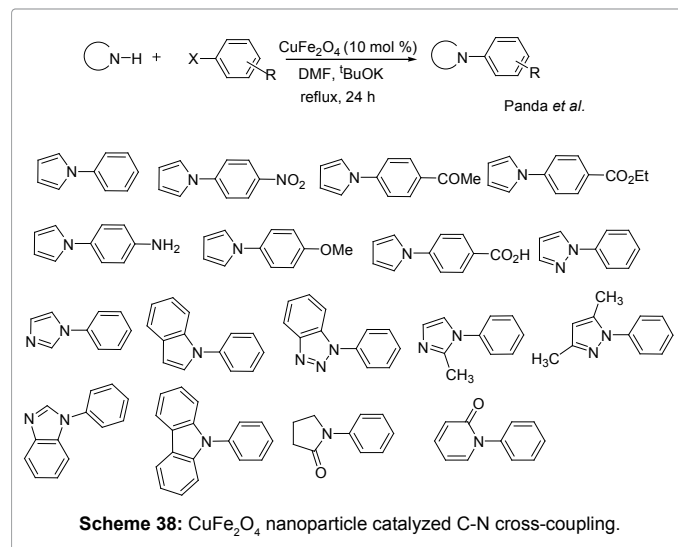


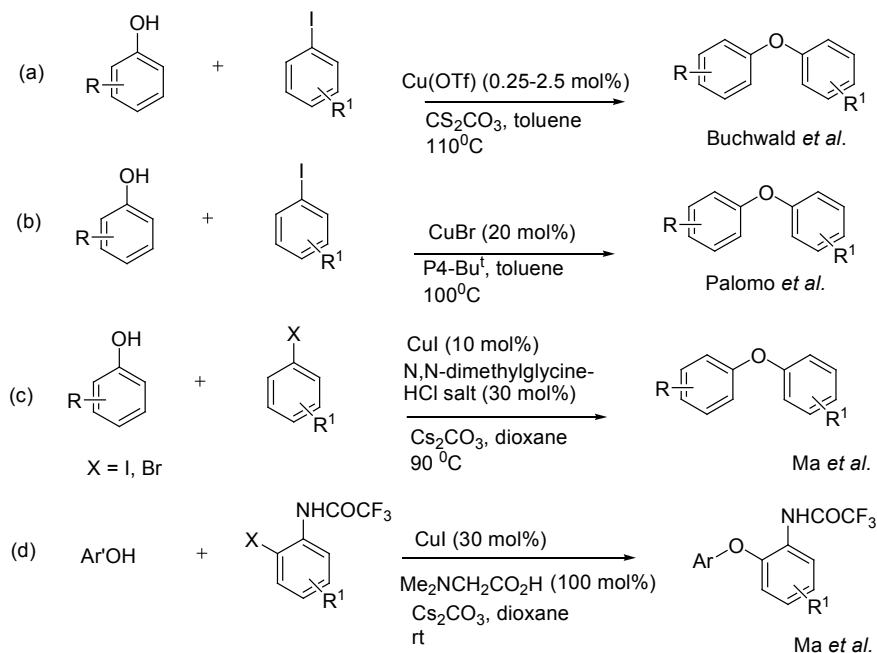
al. [109] employed a mixture of FeCl<sub>3</sub> and CuO in the presence of *rac*-BINOL to promote the *N*-arylation of amines (Scheme 37b). Later, Liu *et al.* [110] reported microwave assisted ligand-free Cu(acac)<sub>2</sub>-Fe<sub>2</sub>O<sub>3</sub> mediated C-N coupling reactions in aqueous DMSO (Scheme 37c). In view to the Cu/Fe-cooperated catalysis reactions, it may be assumed that bimetallic Cu-Fe catalyst would be an economically competitive alternative to the usual copper-ligand combination. In line with this Panda *et al.* [111] developed a magnetically separable catalytic protocol for the *N*-arylation of nitrogen containing heterocycles. They prepared copper ferrite (CuFe<sub>2</sub>O<sub>4</sub>) nanoparticles and used for the *N*-arylation of varieties nitrogen containing heterocycles including pyrrole, imidazole, pyrazole, indole, benzimidazole, carbazole etc. Aryl halides including less reactive aryl chlorides coupled with NH-heterocycles, resulting the *N*-arylated product in moderate to excellent yield [111]. This method was also found to be tolerant to varieties of functional groups of aryl

halides. The magnetic nature of CuFe<sub>2</sub>O<sub>4</sub> nanoparticles is particularly advantageous for easy, quick, and quantitative separation of the catalyst for subsequent use. Negligible leaching of Cu and Fe to the reaction medium made the catalyst environment benign (Scheme 38).

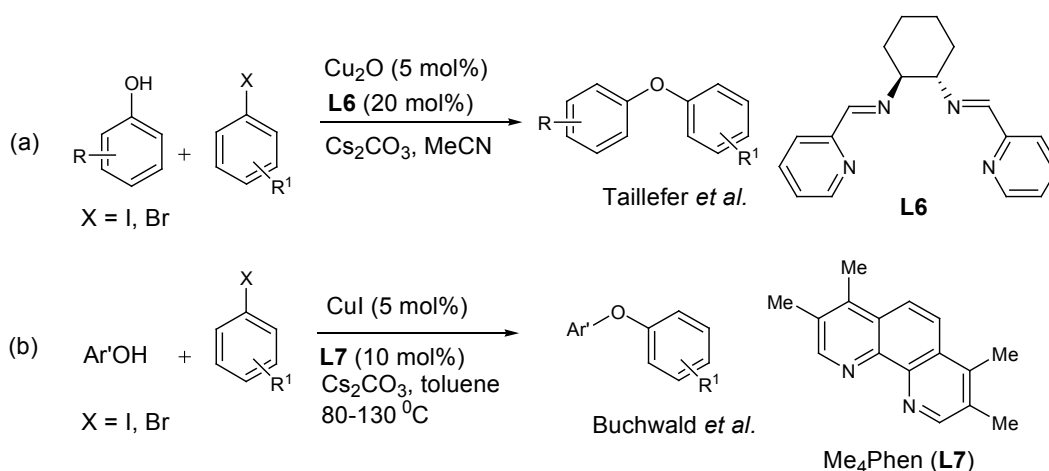
## C-O Cross-Coupling Reactions

Diaryl ethers are found as an important structural motif that are of paramount importance in polymer and life-science industries [112-114]. Indeed, many of the natural products containing diaryl ether bridge, such as antibiotic vancomycin [115] and anti-HIV chloropeptins [116] show significant physiological activities. Consequently, development of new and practical methods for the synthesis of diaryl ethers is of great synthetic value. Owing to their numerous applications in polymer and medicines, many efforts have been devoted for their direct and practical synthesis. The traditional approach involves the Ullmann C-O cross-coupling of alcohols with aryl halides. However, the inherent drawbacks such as high reaction temperature, stoichiometric amount of copper salts and low to moderate yield limit their large scale applications. During the last decade, transition-metals mainly palladium and copper have been utilized for the *O*-arylation reactions. Moreover, the use of toxic and expensive palladium metal reduce their attractiveness for industrial applications. Therefore, less toxic and less expensive metals such as copper and iron have been used for the C-O bond forming reactions [10-13]. In this regard, Buchwald *et al.* [117] described the first case of Cu(OTf)-catalyzed biaryl ether synthesis from the reaction of phenol with unactivated aryl halides (Scheme 39a). The reaction occurs at 110°C using Cs<sub>2</sub>CO<sub>3</sub> as the key reaction element. Later, Palomo *et al.* [118] employed CuBr for similar cross-coupling of phenol with aryl iodides using phosphazene P4-But as base to furnish biaryl ethers at 100°C (Scheme 39b). Subsequently, it has been reported that addition of certain additives, that act as a ligand to the copper catalysts enhance the reaction rate and proceed the coupling under mild conditions [119-121]. In 2003, research group of Ma employed *N,N*-dimethylglycine as ligand towards Cu-mediated C-O cross-coupling reactions between substituted phenols with aryl bromides and iodides in dioxane (Scheme 39c) [122]. Later, the same group carried out the *O*-arylation reactions at room temperature by exploiting the *ortho* effect of NHCOR group to facilitate the Ullmann type C-O coupling reactions under mild reaction conditions (Scheme 39d) [123].





Scheme 39: Ligand-assisted Cu-catalyzed C-O cross-coupling.



Scheme 40: Ligand-assisted Cu-catalyzed C-O cross-coupling.

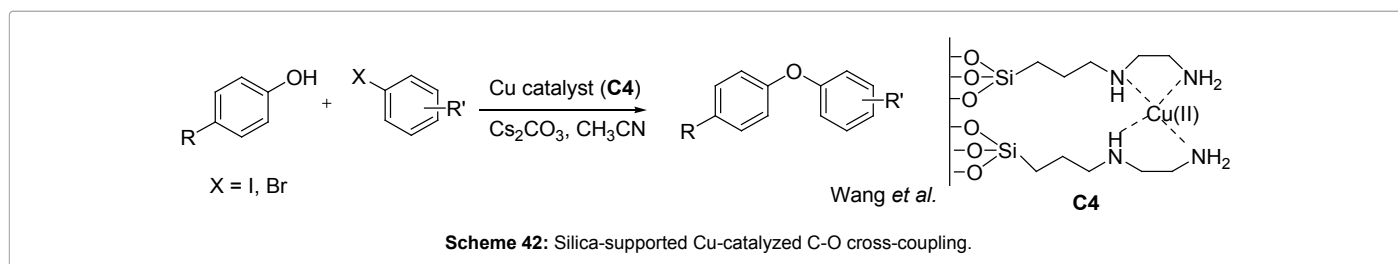
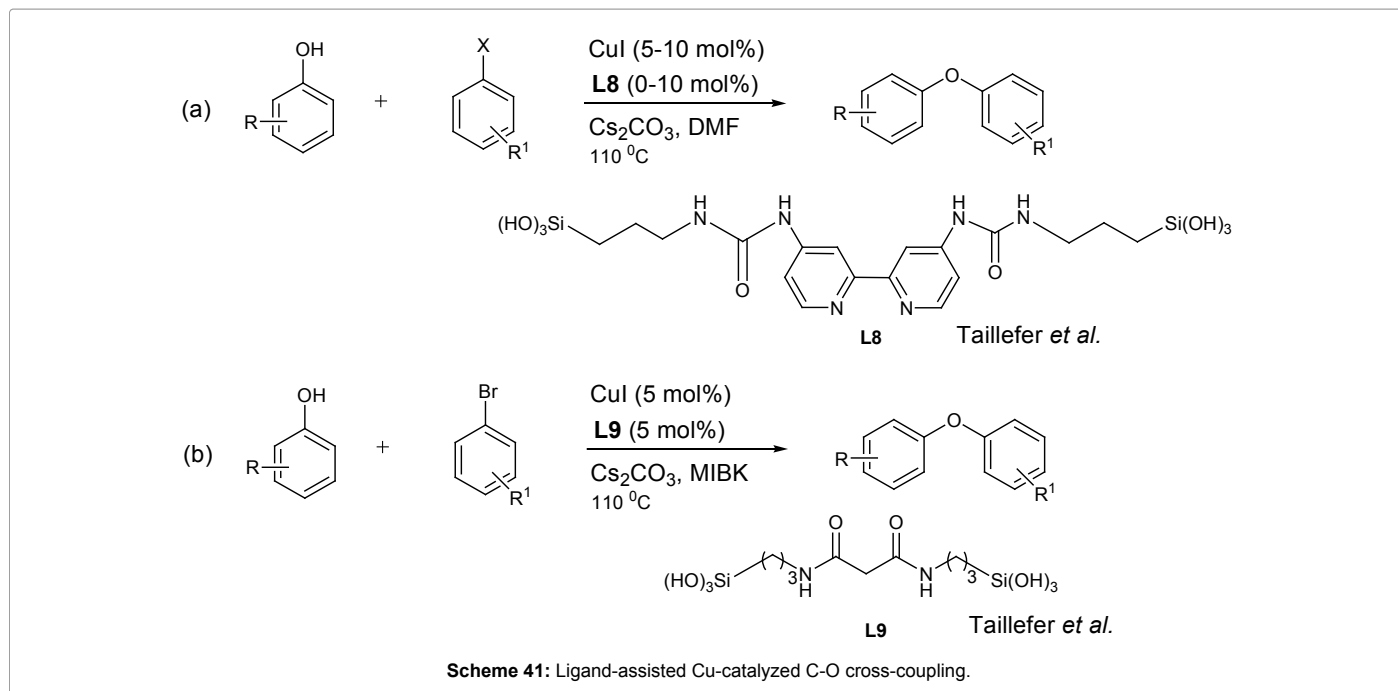
Taillefer described the C-O cross-coupling of phenols with aryl iodides and bromides using catalytic amount of copper (I) oxide and ligand L6. This methodology effectively coupled the sterically hindered phenols with electron-rich aryl halides in acetonitrile (Scheme 40a) [124]. Later, Buchwald employed other ligand such as 3,4,7,8-tetramethyl-1,10-phenanthroline (Me<sub>4</sub>-Phen) (L7) to improve the substrate scope toward the O-arylation reactions. (Scheme 40b) [125].

Subsequently, Taillefer *et al.* synthesized the hybrid silica L8 and used it as a reusable chelating ligand for the Cu-mediated O-arylation reactions (Scheme 41a) [126]. Later, the same group also developed another heterogeneous ligand i.e. hybrid silica L9 which catalyses the O-arylation reaction in the presence of CuI and eco-friendly solvent MIBK (Scheme 41b) [127]. CuO on aluminium support was also

found to be efficient to couple the aromatic and aliphatic alcohols with differently substituted aryl and heteroaryl halides. Catalyst recycling was possible up to 4 consecutive catalytic cycles [128].

The reusable copper catalysts were also employed for the C-O bond forming reactions. For instance, Wang *et al.* [129] applied 3-(2-aminoethylamino)propyl functionalized silica gel immobilized copper catalyst for the C-O cross-coupling reactions between phenols with aryl iodides and bromides in DMSO. The efficiency of the catalyst was found to be high due to the counter anion of the precursor of the catalyst. The silica-supported copper catalyst could recover by simple filtration and reused for successive 10 consecutive trials without significant loss in catalytic activity (Scheme 42).

Although ligand-assisted copper catalysed O-arylation reactions



were successful, the development of ligand-free reactions was also interesting. In this context, recently Mulla et al. first reported a highly efficient and inexpensive method for the synthesis of diaryl ethers using reusable CuFAP as catalyst [130]. They showed that coupling of potassium salt of phenol derivatives with aryl halides including less reactive aryl chlorides and aryl fluorides could occur in NMP at 120°C. The catalyst could recover by filtration and is reusable up to five consecutive cycles without changing the catalytic efficiency (Scheme 43) [130].

Recently, nanocatalysts were also successfully applied for the C-O cross-coupling reactions due to their high surface area and low reduction potential. An interesting example in this line was first published by Kidwai et al.<sup>98</sup> They demonstrated the coupling of phenols with iodo- and bromo arenes using 10 mol% of Cu nanoparticle and Cs<sub>2</sub>CO<sub>3</sub> in CH<sub>3</sub>CN (Scheme 44a) [131]. Punniyamurthy employed the CuO nanoparticles for the synthesis of diaryl ethers in DMSO [132]. Furthermore, CuI [133] as well as Cu<sub>2</sub>O [134] nanocubes were utilized for cross-coupling between phenols with less reactive aryl chlorides (Scheme 44b).

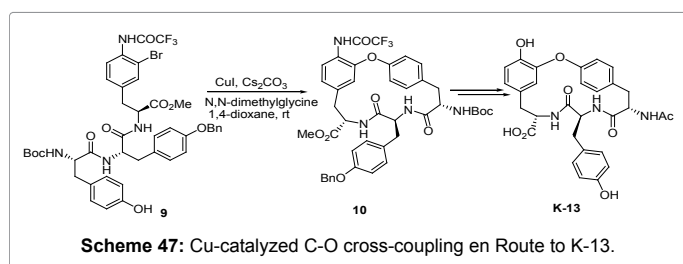
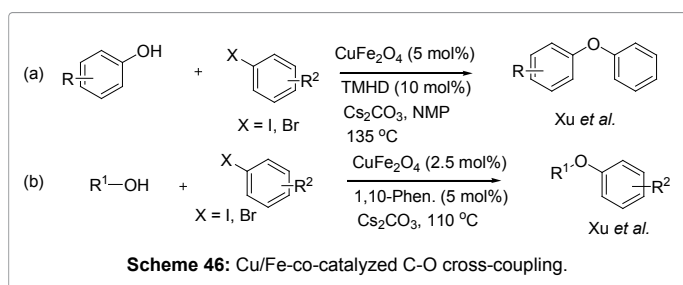
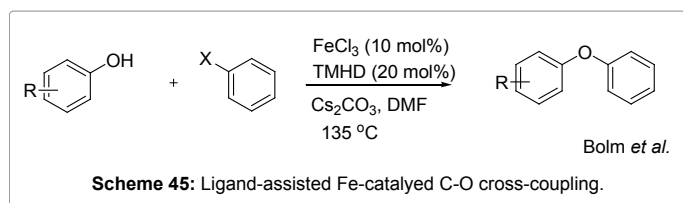
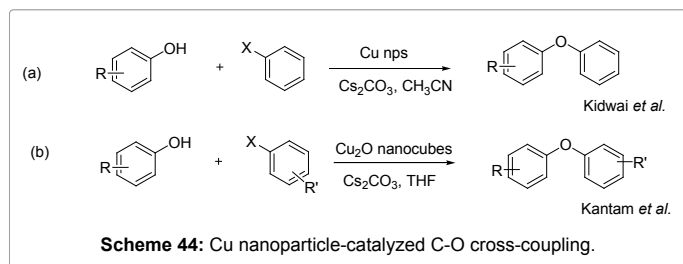
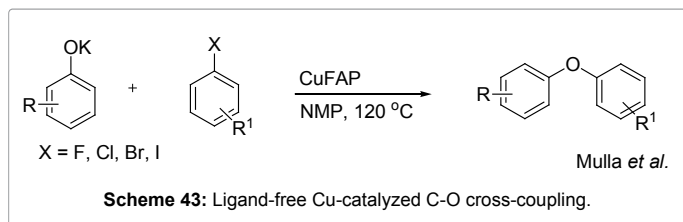
Besides, Fe-based catalysts were also utilized for C-O cross-coupling reactions. For example, Bolm et al. [135] reported an elegant method for the diaryl ether synthesis employing catalytic amount of FeCl<sub>3</sub> in the presence of chelating ligand such as 2,2,6,6-tetramethyl-3,5-heptanedione (TMHD)(Scheme 45).

Cu/Fe-based catalytic systems were found to be effective towards

the coupling of aromatic alcohols with aryl halides but failed towards the O-arylation of aliphatic alcohols. Furthermore, in many cases ligands are essential components to improve the catalytic efficiency of the method. Thus, there was a considerable scope for the development of bimetallic Cu/Fe-cocatalytic systems for the C-O bond forming reactions. In this line, Fu et al. reported CuO/FeCl<sub>3</sub> catalytic system for the coupling of phenols with aryl iodides and bromides [109]. Similarly, Zhang et al. developed an improved methodology for the coupling alcohols with aryl bromides [136]. Recently, Xu et al. reported CuFe<sub>2</sub>O<sub>4</sub> nanoparticle-mediated C-O cross-coupling between substituted phenols with aryl halides, employing TMHD as the ligand and Cs<sub>2</sub>CO<sub>3</sub> as the base in NMP at 135°C (Scheme 46a) [137]. Interestingly, such Cu/Fe catalytic system (ca. CuFe<sub>2</sub>O<sub>4</sub> nanoparticles) found to be effective for the coupling of aliphatic alcohols with aryl halides in the presence of 1,10-Phenanthroline ligand at 110°C (Scheme 46b) [138].

Notably, modified Ullmann C-O cross-coupling reactions were applied for the synthesis of natural and non-natural products. For instance, Ma et al. applied CuI/*N,N*-dimethylglycine towards the synthesis of antitumor agent K-13. The intramolecular C-O cross-coupling of **9** resulted the intermediate **10** which subsequently affords the K-13 (Scheme 47) [123].

Similarly, Cu-promoted C-O bond forming reactions was emerged as key step for the total synthesis of Paliurine F. The coupling of **11** with aryl iodides affords the intermediate **12** which on subsequent steps produces the target molecule Paliurine F (Scheme 48) [139].



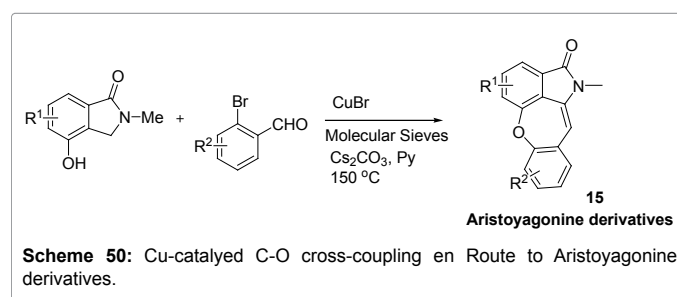
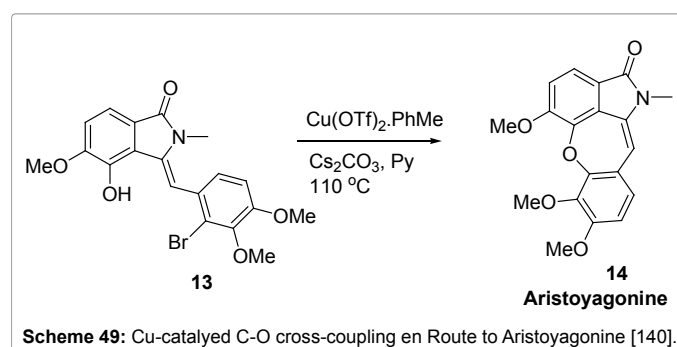
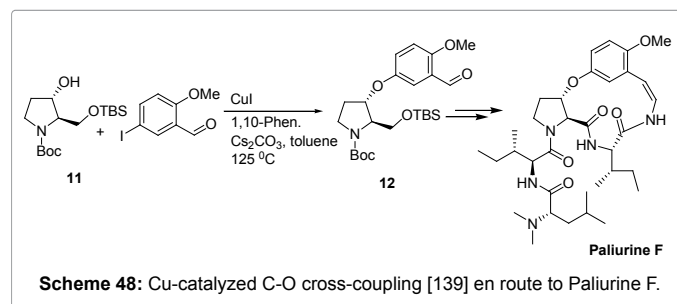
Moreau et al. [140] reported the total synthesis of aristocularine alkaloid aristoyagonine 14 by the intramolecular C-O bond formations from the acyclic precursor 13 using copper triflate as the catalyst in pyridine (Scheme 49).

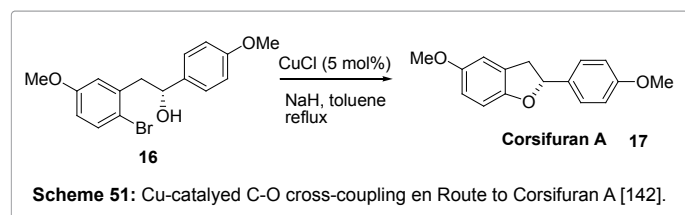
Recently, Cu-mediated etherification/aldol condensation strategy has been applied towards the one-pot synthesis of various aristoyagonine derivatives 15 (Scheme 50) [141].

Jones et al. [142] reported the asymmetric synthesis of Corsifuran A 17, by the intramolecular etherifications of 16 employing 5 mol% of CuCl in refluxing toluene. Interestingly, this copper-catalyzed methodology is found to be better than the similar Pd-catalyzed synthesis of Corsifuran A in terms of yield and enantiomeric excess (Scheme 51).

## C-S Cross-Coupling Reactions

The formation of C(aryl)-S bond is of great importance because of the prevalence of these bond in many molecules that are of pharmaceutical and material interest [143-145]. For example, biaryl sulfides have been found as a common structural motifs in many drug candidates and have been used for the treatment of various diseases such as Alzheimer's and Parkinson's diseases, [146,147] human immunodeficiency virus diseases, [148] and cancer [144] etc. Traditionally, the C(aryl)-S bonds are synthesized under harsh reaction conditions such as elevated temperature (200°C) in toxic, high boiling polar solvents like HMPA. Alternatively, these sulfides can be prepared by the reduction of aryl sulfones and sulfoxides using strong reducing agents like DIBAL-H or LiAlH<sub>4</sub> [149,150]. To overcome aforementioned limitations, transition-metal catalysts are employed for various C-S bond forming reactions [151,152]. Evidently, among the TM-catalyzed coupling reactions, C-S cross-coupling received less attention in comparison to C-N and C-O cross-coupling reactions, because: (i) thiols are prone to undergo oxidative S-S coupling reactions to undesired disulfides and (ii) strong coordinating properties of organic sulfur compounds, often make the catalyst ineffective (catalyst poison) [153]. Transition metals such as Pd, Ni etc. were extensively used for the C-S bond forming reactions. However, the cost and toxicity of the above metals limit their large scale applications particularly in pharmaceutical industry. Thus, cheap and less toxic Cu/Fe-based catalysts have been developed for the C-S cross-





coupling reactions. Suzuki et al. first demonstrated the reaction between aryl thiols with aryl iodides using CuI in hexamethylphosphoramide (HMPA) to get moderate to good yield (60-77%) of corresponding aryl sulfides (Scheme 52a) [154]. When Schwesinger's phosphazene base (P<sub>2</sub>Et) was used as a ligating agent, yield of aryl sulphide was increased substantially (Scheme 52b) [155].

Numerous other ligands were used by several researchers along with copper salt to expand the scope of C-S cross-coupling reactions. Evidently, Venkataraman et al. utilized bidentate ligands such as neocuprine [156] and 1,10-phenanthroline [157] along with copper salt for the cross-coupling of thiols with aryl halides and vinyl halides, respectively (Scheme 53). Vinyl sulfides were also synthesized using *cis*-1,2-cyclohexanediol as the ligand and CuI as the catalyst [158,159].

Buchwald et al. [160] developed CuI/ethylene glycol for the S-arylation of thiol derivatives at lower temperature (80°C) though excess of ethylene glycol were used (Scheme 54a). Later, they applied the above catalytic systems toward the cross-coupling of aryl thiols with 6-halogenoimidazo-[1,2]pyridines (Scheme 54b) [161].

Similarly, a tridentate oxygen containing ligand like 1,1,1-tris(hydroxymethyl)ethane (L10) have been used for the C-S cross-coupling between thiols with aryl iodides in a mixture of DMF and dioxane (Scheme 55a) [162]. Scope of the coupling reactions was further expanded by choosing oxime-phosphine oxide (L11) as a ligand. A range of thiols including both aliphatic and aromatic thiols coupled with activated and unactivated aryl iodides to form the alkyl-aryl and diaryl sulfides in good to excellent yield (Scheme 55b) [163]. Later, Verma et al. reported CuI/benzotriazole catalytic systems for coupling the thiols with less reactive aryl bromides (Scheme 55c) [164]. Subsequently, various amines including *trans*-1,2-diaminocyclohexane [165], BINAM [166,167] etc. have been utilized successfully as a ligand to promote the S-arylation reactions.

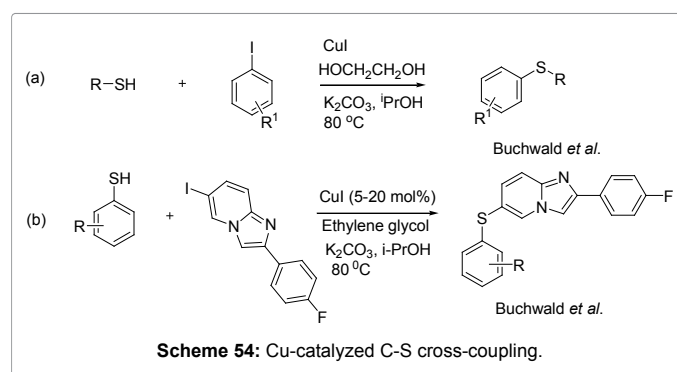
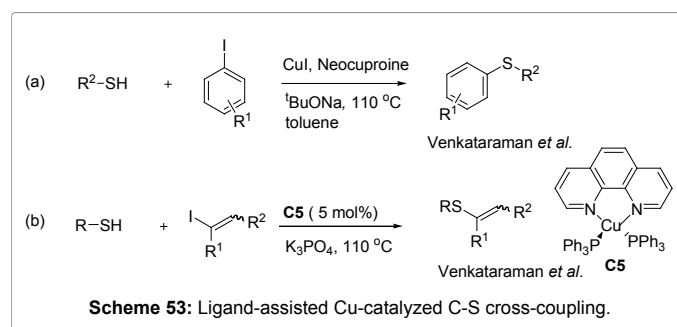
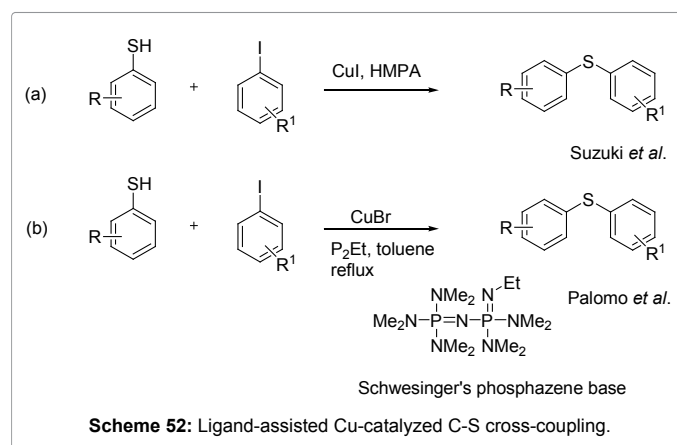
Additionally, ligand-free S-arylation reactions were also developed owing to the advantages over purification problem caused by the ligands. For instance, van Koten illustrated the C-S cross-coupling of thiols with aryl halides in the presence of CuI in NMP at 100°C (Scheme 56a) [168]. Vinyl sulfides were also prepared by Liu using decarboxylative C-S cross-coupling reaction between arylpropionic acids with thiols (Scheme 56b) [169]. Punniyamurthy et al. [170] reported a ligand-free copper-promoted S-arylation reactions for the synthesis of 2-(arythio) arylcyanamides from 2-(iodoaryl)thioureas and aryl iodides in DMSO (Scheme 56c). They also utilized CuO nanoparticles for the C-S cross-coupling reaction between thiols with aryl iodides in DMSO at 90°C (Scheme 56d) [171]. Later, CuI nanoparticles were expanded for the S-arylation reactions in water by Xu et al. (Scheme 56e) [172]. Recently, Fu and Peters developed a ligand-free photoinduced C-S coupling between thiols with aryl halides including less reactive aryl chlorides using catalytic amount of CuI under mild reaction conditions [173].

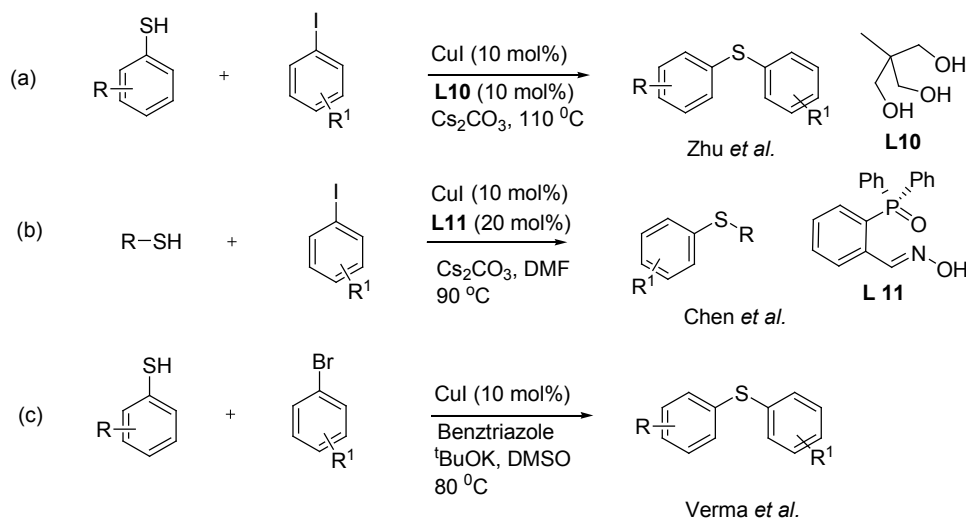
Recently, CuO nanoparticles have been employed for the synthesis of diaryl sulfides using thiourea [174] and ethyl potassium xanthogenate [175] as the sulfur surrogates. Use of thiourea resulted

symmetrical sulfides whereas ethyl potassium xanthogenate produced the unsymmetrical diaryl sulfides in DMSO (Scheme 57). A microwave-assisted ligand-free copper nanoparticle-mediated S-arylation of thiols with aryl iodides have been reported by Ranu et al. (Scheme 58) [176].

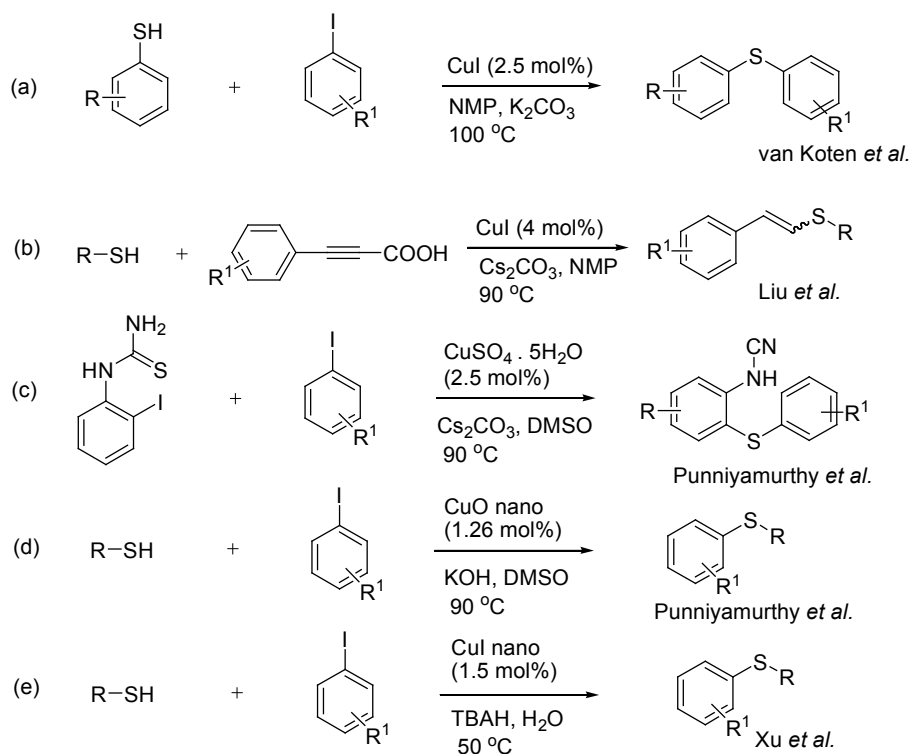
As an alternative to Pd-catalyst, iron-catalysts were also extensively used for C-S cross-coupling reaction. The most significant advances in this direction were made by Bolm et al. They found that the combination of FeCl<sub>3</sub> and DMEDA served as an effective catalytic system for the coupling of numerous thiols with aryl iodides (Scheme 59a) [177]. Moreover, in a competent report Buchwald and Bolm observed that reactions with FeCl<sub>3</sub> in certain cases be significantly affected by trace quantities of other metals, particularly copper [178]. Tsai et al. [179] were also utilized ligand L12 to carry out the coupling reactions in aqueous medium (Scheme 59b).

The synergistic effects of Cu and Fe on C-S cross-coupling reactions were investigated considering the fact that iron has the ability to suppress the disulfide formations. Liu et al. [180] disclosed





**Scheme 55:** Ligand-assisted Cu-catalyzed C-S cross-coupling.

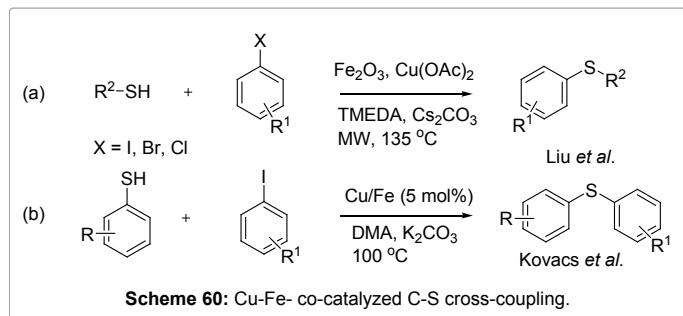
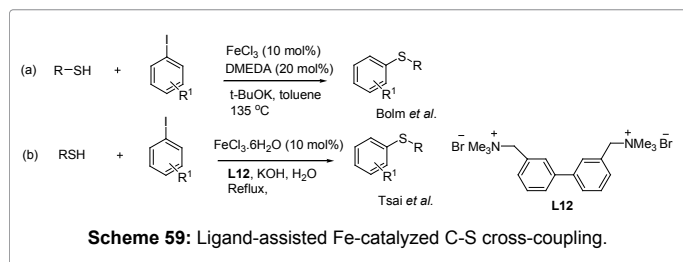
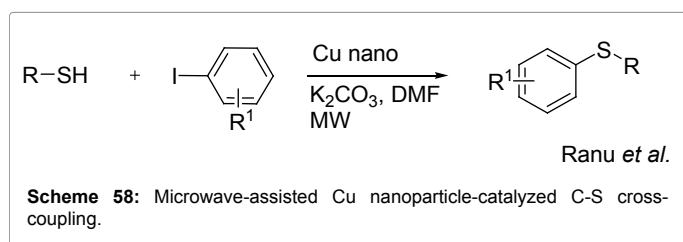
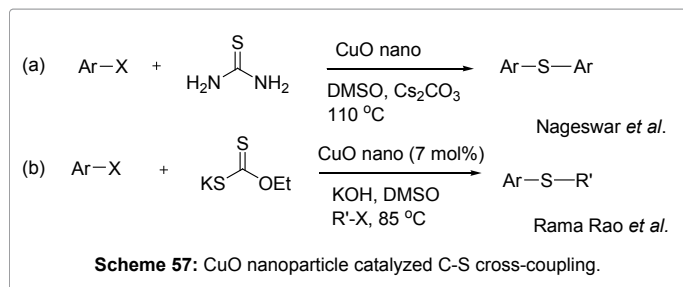


**Scheme 56:** Ligand-free Cu-catalyzed C-S cross-coupling.

ligand-assisted  $\text{Cu}(\text{OAc})_2\text{-Fe}_2\text{O}_3$  co-catalytic system for the coupling of thiol derivatives with aryl and heteroaryl halides under microwave irradiations (Scheme 60a). Recently, Kovacs and Novak developed copper on iron as heterogeneous catalyst for the S-arylation of thiols with aryl iodides (Scheme 60b) [181].

In this line, Panda *et al.* [182] and Nageswar *et al.* [183] exploited the catalytic activity of magnetic copper ferrite nanoparticles in S-arylation reactions. Both aliphatic and aromatic thiols coupled with the aryl halides including less reactive aryl chlorides, leading to the

corresponding aryl-alkyl and diaryl sulfides in good to excellent yield (Scheme 61) [184]. Advantages of using copper ferrite nanoparticle are: (i) this method is simple and results in high yield of the S-arylated product; (ii) due to the magnetic nature of the catalyst, it can be separated quantitatively; (iii) the catalyst can be reusable for consecutive cycles (minimum three) without loss of efficiency; (iv) this catalytic system does not require any additional ligand to promote the coupling reaction and this method is tolerant to a wide variety of functional groups attached to both thiols as well as halides. Furthermore Panda



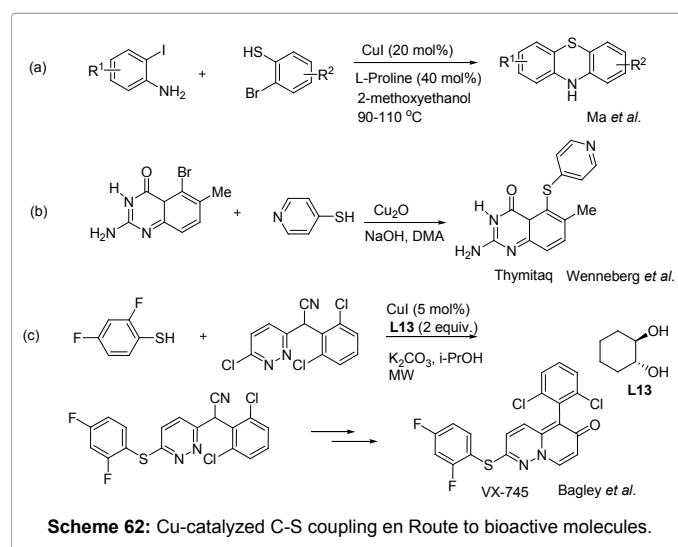
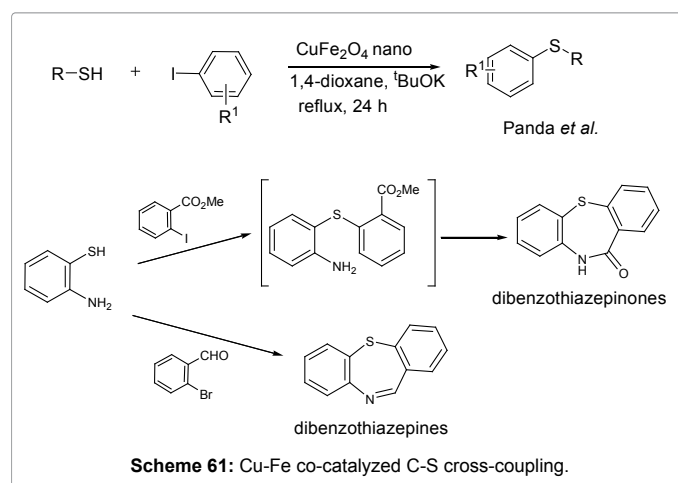
*et al.* exploited the efficiency of developed catalytic system for the one-pot synthesis of tricyclic dibenzothiazepine derivatives by a tandem C-S/C-N bond forming reactions between 2-aminothiophenols with 2-bromobenzaldehydes. (Scheme 61) [182]. It is worthy to mention that benzo-fused thiazepines having medium-ring (6-7-6) structures show pronounced therapeutic effect on the central nervous system and are particularly active as antidepressants, antiemetic, analgesics and sedatives. Successful examples include quetiapine and clothiapine, which are clinically used for the treatment of bipolar and psychiatric disorders (Figure 4) [184-187].

Cu/Fe-mediated C-S cross-coupling reactions were shown to be applied for the synthesis of a number of complex molecules. For example, Naus *et al.* [188] reported CuI/pyridine catalytic system for the synthesis of triazine substituted arylthioglycosides in MeCN. Ma *et al.* [189] developed a Cu-mediated synthesis of substituted phenothiazines by a cascade C-S and C-N bond forming reactions (Scheme 62a). This method has been employed successfully for the synthesis of promazine drugs like chlorpromazine, trifluorpromazine

and acepromazine in good yield. Wennerberg *et al.* [190] prepared the anticancer agent thymitaq in large scale by copper-mediated coupling between halide and 4-mercaptopyridine (Scheme 62b). Bagley *et al.* reported a copper mediated methodology for the synthesis of P38 $\alpha$  MAPK Clinical Candidate VX-745 by C-S coupling reaction (Scheme 62c) [191].

### C-Se Cross-Coupling Reactions

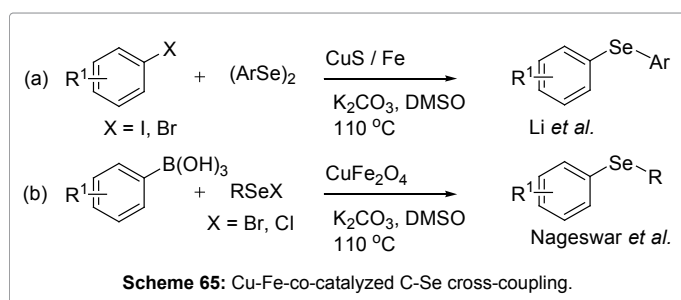
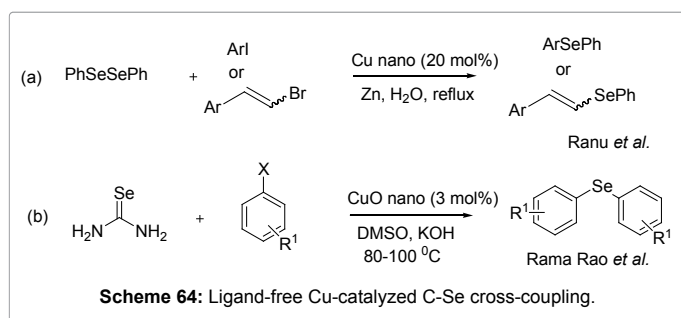
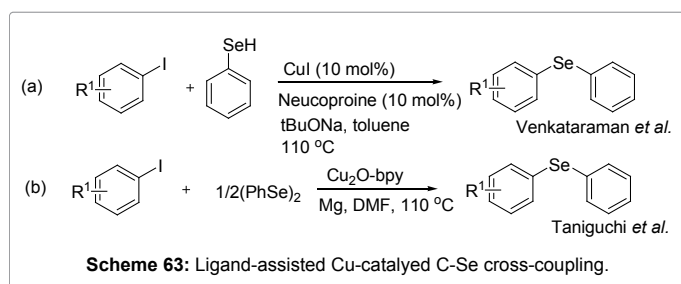
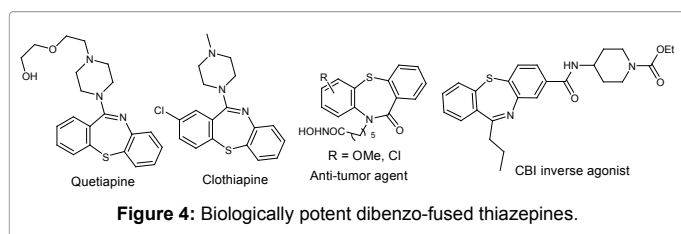
Organoselenium compounds act as a versatile reagent in organic synthesis and catalysis [192-195]. The biological properties of these compounds received increased attention due to their antioxidant, antitumor, antimicrobial, anticancer, and antiviral properties [196-199]. As compared to other type of C-hetero bond forming reactions, C-Se cross-coupling reactions have been less reported. Venkataraman and Gujadhur [200] first disclosed a ligand-assisted copper-promoted methodology towards the coupling between phenyl selenols with electron rich aryl iodides in refluxing toluene (Scheme 63a). Later, Taniguchi [201] demonstrated the efficiency of Cu<sub>2</sub>O/bpy/Mg catalytic system for the C-Se bond forming reactions. A range of electron-donating and -withdrawing aryl and heteroaryl iodides coupled with the diphenyldiselenides, affording the unsymmetrical diaryl selenides in good yield. However, the major drawback associated with the Taniguchi's protocol was the extended reaction time (18-72 h) (Scheme



63b). When the reaction was carried out in the presence of microwave rate of the reaction was accelerated [202].

Recently, nanoparticles were employed for the C-Se bond forming reactions. For example, Ranu et al. [203] reported the copper nanoparticle-mediated synthesis of aryl and vinyl selenides in aqueous medium. Coupling of diphenyldiselenides and *E*-vinyl bromides resulted (*E*)-vinyl selenides, whereas with *Z*-vinyl bromides, a mixture of (*E*-) and (*Z*)-isomers were obtained (Scheme 64a) [204]. Subsequently, Rama Rao et al. reported the CuO nanoparticle mediated C-Se coupling reactions [204]. Both electron-donating and -withdrawing aryl halides effectively coupled with the diphenyldiselenides, resulting aryl selenides in good to excellent yield. Later, they utilized the selenourea as a coupling partner for the synthesis of symmetrical selenides (Scheme 64b) [205].

Subsequently, Li et al. [206] reported that the CuS catalyzed coupling reactions of aryl halides and diaryl diselenides were accelerated by the addition of Fe powder leading to diarylselenides



in good to excellent yields. Notably, incorporation of iron not only prevents the agglomeration of catalyst but also reduce the CuS to more active Cu<sub>2</sub>S (Scheme 65). Very recently, Nageswar et al. [207] exploited the magnetic copper ferrite nanoparticles for the C-Se cross-coupling reactions by coupling the phenyl selenyl bromides and chlorides with aryl boronic acids in recyclable PEG-400 medium at 80°C (Scheme 65b).

## Conclusion and Future Prospects

In this review, we have summarized copper/iron-mediated C-C, C-hetero cross-coupling reactions. A number of ligand-assisted as well as ligand-free catalytic systems have been described. The synergistic effects of copper and iron in cross-coupling reactions have also been exemplified. The catalytic systems showed good functional group tolerance with wide substrate scope and applied towards the synthesis of various natural and non-natural products of biological significance. Despite the significant development on Cu/Fe catalyzed cross-coupling reactions, the mechanism of the reaction is still little explored. More concern is needed to explore the exact pathway of the coupling reaction. Furthermore, development of catalyst which can promote the bond formation between the coupling partners in green solvent or in the absence of solvent to reduce the environmental hazard is promising. Besides, development of more efficient catalytic system is needed which can use less reactive aryl chlorides or sulfonates for coupling reactions to produce high yield of the product.

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