

Review

# On the Current Status of Ullmann-Type *N*-Arylation Reactions Promoted by Heterogeneous Catalysts

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**Abstract:** Ullmann-type C–N heterocoupling reactions have been applied for the syntheses of *N*-arylated amines. In the past decade, transition metal-catalyzed *N*-arylations have been recognized as particularly efficient procedures for the preparation of nitrogen-containing aromatic systems. These reactions typically carried out under optimized conditions, have also been found to be suitable for the synthesis of complex molecules with other functional groups, including natural products, drugs, or pharmaceuticals. Most importantly, copper-catalyzed *N*-arylations have been studied and employed in the total synthesis of biologically active compounds. The construction of fused *N*-heterocyclic compounds also remained the subject of extensive research because of their potential applications in drug discovery and the development of functional materials. The aim of this review is to summarize the recent progress in the synthetic applications of Ullmann-type *N*-arylation reactions performed in heterogeneous systems. In particular, the utilization of copper and palladium species immobilized on various support materials, modified by surface functionalization, has been discussed and evaluated.

**Keywords:** Ullmann reaction; *N*-arylation; heterocoupling; palladium; copper; magnetic nanoparticle; immobilization; functionalization



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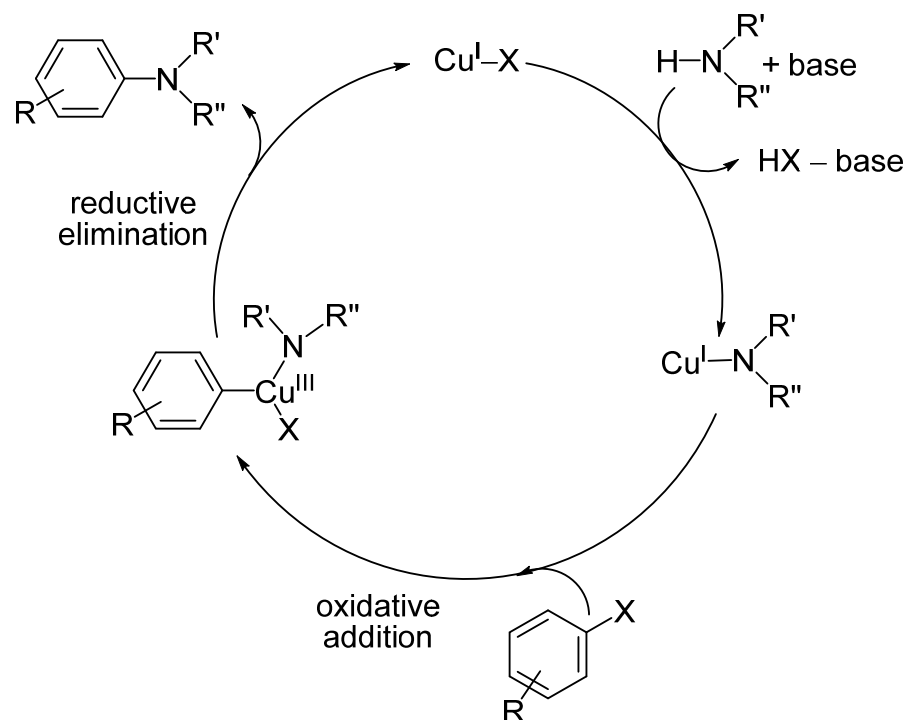
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## 1. Introduction

Ullmann-type *N*-arylations have long been employed for the synthesis of various molecules and intermediates, suitable for a large number of biological, medicinal, and pharmaceutical applications, and, therefore, they belong to the most important transition metal-catalyzed cross-coupling reactions [1–3]. However, copper-catalyzed *N*-arylations have often been found to require harsh reaction conditions and displayed a poor tolerance towards other functional groups [4]. In the past decade, the efficiency of copper-catalyzed Ullmann reactions has been considerably improved by applying novel copper sources, specific ligands, and additives [5–8]. Several mild and sustainable methods have been developed for these reactions, including the *N*-arylations of indoles and other heterocycles [9–13]. The reaction pathway suggested for the Ullmann-type C–N heterocoupling reaction is indicated in Scheme 1. The reaction of an amine with the active Cu<sup>I</sup> species is followed by the oxidative addition of an aromatic halide, producing an aryl complex, in which the oxidation state of copper has changed to Cu<sup>III</sup>. The final step is reductive elimination, which releases the coupling product, containing a new C–N bond, and regenerates the active Cu<sup>I</sup> species, which is able to participate in another catalytic cycle.

Although the homogeneous *N*-arylations catalyzed by copper complexes afforded high product yields and selectivities, problems associated with the recovery and recycling of these complexes initiated further studies focused on the development of more efficient and recyclable heterogeneous catalysts. Novel synthesis procedures based on the immobilization of catalytically active metal species or organometallic complexes on various support materials provided reusable heterogeneous catalysts with improved performances [14].

Whereas recent studies on the Ullmann homocoupling reactions clearly indicated the predominance of heterogeneous Pd catalysts [15], C–N heterocoupling reactions have still been preferably conducted by using more readily available and less toxic Cu-based catalysts [16–21]. The subject of the current review is the presentation of the recent progress achieved in the Ullmann-type *N*-arylation reactions performed in heterogeneous systems, including the utilization of Cu and Pd-based catalysts and magnetic nanoparticles.

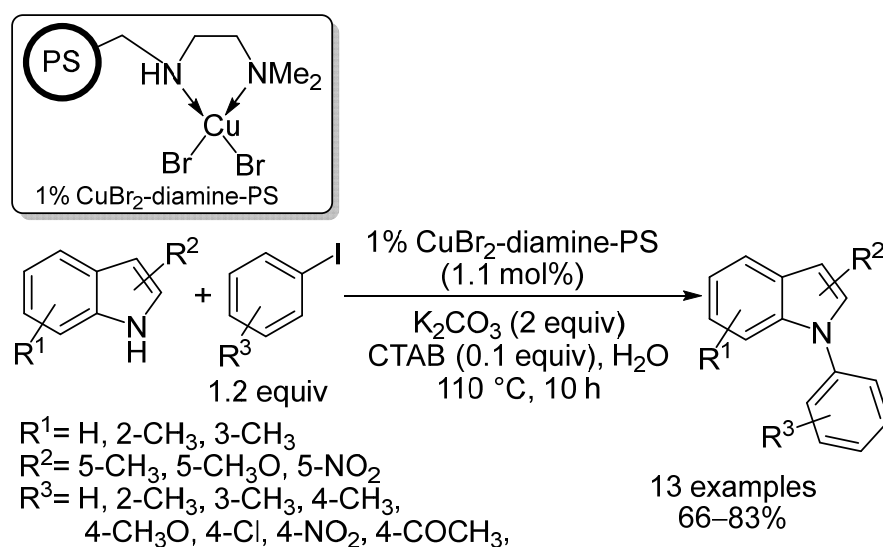


**Scheme 1.** The reaction mechanism proposed for the Ullmann-type *N*-arylation.

## 2. Results

### 2.1. Copper-Based Catalysts

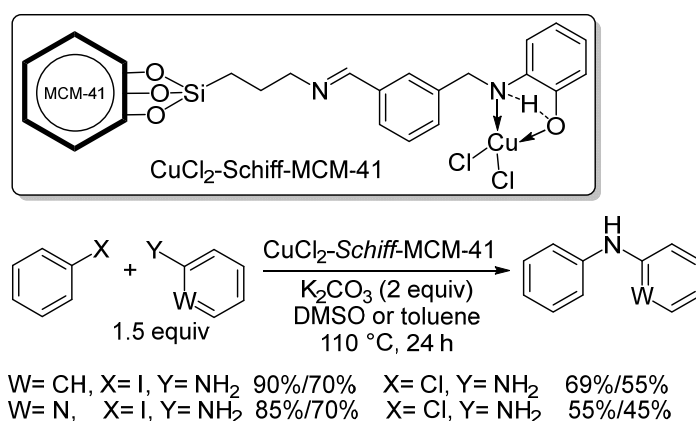
As related to its inert character, low cost, and facile functionalization, polystyrene has been considered one of the most popular polymer support materials of immobilized metal complexes, which have been found to be active and reusable heterogeneous catalysts of C–C coupling reactions performed in aqueous systems [22–24]. Mandapati et al. synthesized a polymer anchored  $\text{Cu}^{\text{II}}$  *N,N*-dimethylethylenediamine complex, to be applied as a catalyst for the *N*-arylations of indoles [25]. The immobilized complex was prepared in an acetonitrile solution of chloromethylated polystyrene (PS) in the presence of *N,N*-dimethylethylenediamine and NaI. After heating the mixture for 48 h and drying, the polymeric ligand was treated with ethanol and  $\text{CuBr}_2$ , which afforded a ligand-functionalized polystyrene-supported  $\text{CuBr}_2$  complex. Structural characterization of the product was performed by FTIR, energy dispersive X-ray spectroscopy (EDX), TGA, SEM, and atomic absorption spectroscopy (AAS). The amount of copper incorporated in the polymer was found to be 6.22 wt%. The ligand-polymer interaction was confirmed by FTIR spectroscopy, and the formation of the polymer-supported  $\text{CuBr}_2$  complex was revealed by EDX analysis. The sample was examined as a catalyst in the *N*-arylation reaction of iodobenzene with indole. The reactions were performed in water at 110 °C for 10 h, in the presence of 0.03 mmol of catalyst,  $\text{K}_2\text{CO}_3$  as a base, and cetyltrimethylammonium bromide (CTAB). The results are shown in Scheme 2.



**Scheme 2.** *N*-Arylations of indoles, promoted by a  $\text{CuBr}_2$  complex catalyst.

It was established that the substituent had only a minor effect on the product yield. Recycling of the catalyst was investigated for the reaction of iodobenzene with indole, and decreasing yields were obtained (yield: 82–74%, avg. 78.5%, four runs), together with a rather significant Cu leaching of 0.2% and 5%, observed after the first and fourth reaction, respectively. Furthermore, a hot filtration test indicated that  $\text{CuBr}_2$ -diamine-PS may be considered as a heterogeneous catalyst.

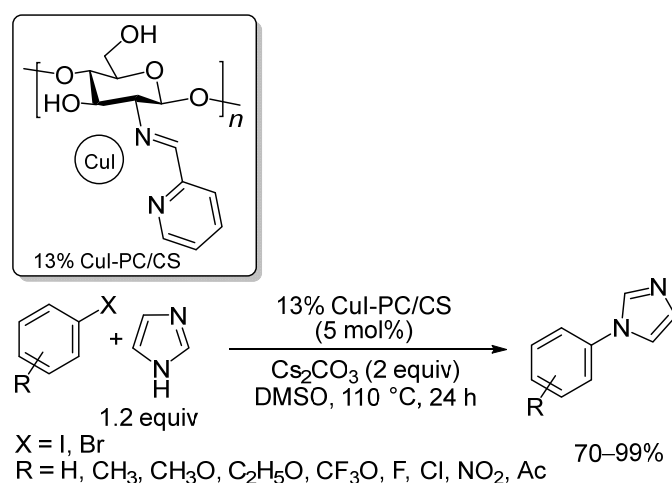
As related to their high surface areas, large pore volumes, and regular pore structures, ordered mesoporous silicas have been considered excellent support materials for metal complexes, cations, and nanoparticles. The structure of MCM-41, a mesoporous molecular sieve, is composed of uniform hexagonal pores, which renders it a favorable host material of catalytically active metal species [26–30]. Rangappan et al. synthesized a Schiff base  $\text{Cu}^{\text{II}}$  complex supported on MCM-41, to be employed as a catalyst for the Ullmann-type *N*-arylation reaction [31]. MCM-41 was synthesized from tetraethylorthosilicate (TEOS) and cetyltrimethylammonium bromide (CTAB), followed by calcination at 550 °C for 5 h. The Schiff base was prepared according to a previous synthesis procedure [32] from the solutions of 3-aminopropyltrimethoxysilane (APTES), terephthalaldehyde, and 2-aminophenol, and the imine groups derived from the latter compounds via condensation provided anchoring sites for the precursor  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ . The final step was the addition of the siloxane-functionalized  $\text{Cu}^{\text{II}}$  complex to MCM-41 under an  $\text{N}_2$  atmosphere, followed by stirring for 24 h. Structural characterization of the product,  $\text{CuCl}_2$ -Schiff-MCM-41, was performed by TGA, SEM, XRD, EDX,  $\text{N}_2$  sorption, and FTIR studies. SEM images indicated that no significant changes occurred in the morphology of MCM-41 after immobilization, and the formation of the  $\text{CuCl}_2$ -Schiff-MCM-41 complex was confirmed by EDX spectra and  $\text{N}_2$  sorption isotherms. The catalytic investigation of the sample comprised the *N*-arylation reactions of aniline and 2-aminopyridine with aromatic halogen derivatives. The reactions were carried out at 110 °C for 24 h by using  $\text{K}_2\text{CO}_3$  as a base and either DMSO or toluene as a solvent. The amount of the catalyst was not specified. As shown in Scheme 3, the highest product yields were experienced in DMSO, for the reactions of iodobenzene (90% and 85%, obtained for the heterocoupling of aniline and 2-aminopyridine, respectively). The FTIR spectra of the recovered catalyst proved to be similar to that of the pristine sample, indicating that no structural deterioration occurred under reaction conditions.



Percentage data indicate DMSO/toluene ratios.

**Scheme 3.** The catalytic performance of  $CuCl_2$ -Schiff-MCM-41 in C–N heterocoupling reactions.

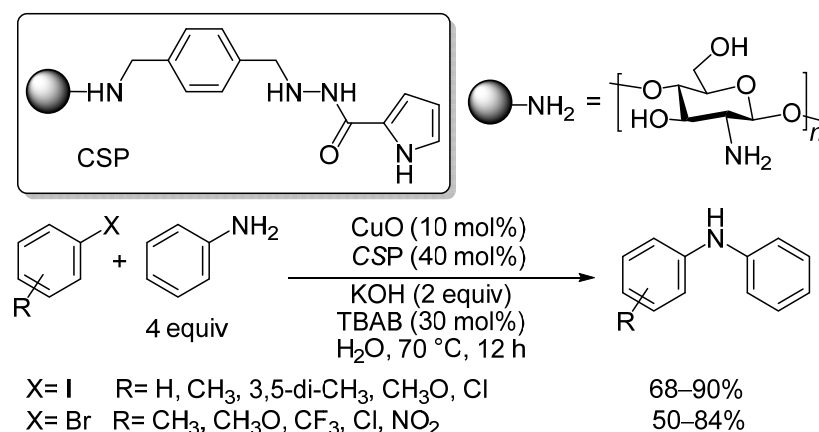
Polysaccharides have been found to be important bio-resources on account of their various functional groups, as well as their biodegradable, renewable, and eco-friendly nature [33,34]. Among these materials, chitosan (CS) has been frequently applied as a catalyst support material, as related to its high affinity to metals, water-soluble character, and large number of amino groups, which make it suitable for chemical modification [35–37]. Chitosan-supported Cu catalysts have been successfully applied for Ullmann-type heteroarylations [38], but only a few examples have been reported for the utilization of functionalized chitosan materials in these kinds of reactions [39,40]. Recently, Ge et al. synthesized a functionalized chitosan-supported copper complex to be applied as a catalyst in the Ullmann-type *N*-arylation reaction [41]. The amino groups of chitosan were modified by pyridine-2-carboxaldehyde (PC) in methanol, and the modified chitosan was suspended in an acetonitrile solution of CuI under stirring, followed by purification. The synthesis product, CuI-PC/CS, was characterized by various instrumental techniques. The Cu loading of the sample was found to be  $2.05 \text{ mmol g}^{-1}$  by ICP analysis. FTIR spectra indicated that the introduction of pyridine-2-carboxaldehyde into CS resulted in the formation of a Schiff base, and energy disperse spectra (EDS) revealed the successful chelate complex formation of CuI with PC/CS. XPS patterns demonstrated characteristic peaks at the binding energies 932.3 and 952.1 eV, assigned to the Cu  $2p_{3/2}$  and  $2p_{1/2}$  levels, which referred to the occurrence of  $Cu^I$  species. The catalytic performance of the CuI-PC/CS sample was studied in the Ullmann C–N heterocoupling reactions of aryl halides with imidazole. The reactions were performed at  $110 \text{ }^\circ\text{C}$  for 24 h, by using 5 mol% of catalyst,  $Cs_2CO_3$  as a base, and DMSO as a solvent. The results are displayed in Scheme 4.



**Scheme 4.** C–N heterocoupling reactions catalyzed by CuI-PC/CS.

The isolated yields obtained for 4-substituted iodobenzenes containing electron-donating substituents (96–98%) proved to be higher than those with electron-withdrawing substituents (70–89%), and 2-substituted aryl halides also afforded substantial yields of 83–85%. The heterocoupling of chlorobenzene did not take place. The catalyst could be reused four times without an appreciable deactivation (yield: 99–95%, avg. 97%, five runs), and the copper content of the recovered catalyst was  $1.89 \text{ mmol g}^{-1}$ , indicating that leaching of the active copper species was negligible.

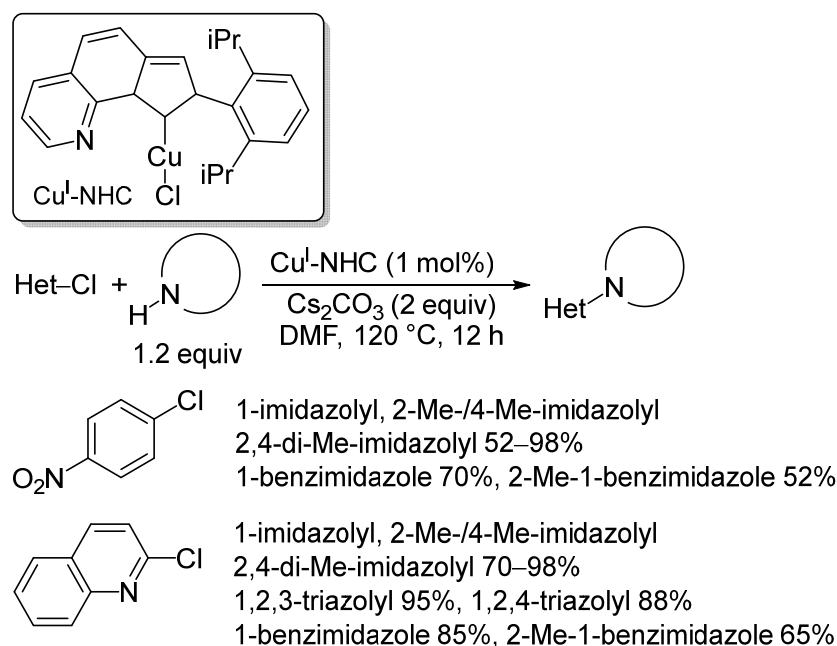
In a related study, based on previous results obtained for the combination of pyrrole-2-carbohydrazide ligands with copper sources applied as catalysts in C–N heterocoupling reactions [42], Zhu et al. investigated the catalytic application of functionalized chitosan in *N*-arylation reactions [43]. Chitosan-supported pyrrole-2-carbohydrazide (CSP) was prepared via the reaction of chitosan with 4-(diethoxymethyl)benzaldehyde, followed by reduction with  $\text{NaBH}_4$ . The product was subsequently treated with 6 M HCl, and then a methanol solution of pyrrole-2-carbohydrazide was added, and the reaction mixture was treated under reflux conditions for 12 h. Finally, another reduction was performed by  $\text{NaBH}_4$ . The functionalized chitosan was combined with CuO and applied as a catalyst for the heterocoupling reactions of aniline with various aryl halides. The results are indicated in Scheme 5.



**Scheme 5.** CuO-CSP catalyzed C–N heterocoupling reactions.

In a recycling study performed for the C–N coupling reaction of 4-iodoanisole with benzylamine, a significant activity decrease was experienced (yield: 90–50%, avg. 65.5%, six runs), which was attributed to leaching of the active copper species.

Owing to their  $\sigma$ -donor characters, *N*-heterocyclic carbenes (NHCs) are considered as versatile ligands with a pronounced affinity for the formation of Cu complexes [44]. Although a number of NHC–Cu complexes have been synthesized and employed in catalytic reactions [45,46], less attention has been focused on their utilization in Ullmann-type *N*-arylations. The application of a  $\text{Cu}^{\text{I}}$  complex containing a 1,10-phenanthroline analog NHC ligand for the heterocoupling of chlorobenzenes with nitrogen heterocycles has been reported by Zeng and Liu et al. [47]. The  $\text{Cu}^{\text{I}}$  complex was synthesized from 1,8-naphthyrido[1,2-a]-(2',6'-diisopropylphenyl) imidazolium chloride [48] via the addition of CuCl and  $\text{K}_2\text{CO}_3$  in acetone, followed by heating at  $60^\circ\text{C}$  for 24 h under an  $\text{N}_2$  atmosphere. Structural characterization of the resulting  $\text{Cu}^{\text{I}}$ -NHC complex was performed by  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy and XRD. The  $\text{Cu}^{\text{I}}$ -NHC complex was applied as a catalyst in the *N*-arylation reactions of 4-nitrochlorobenzene with various *N*-heterocycles, including imidazole, methylimidazole, 1,2,4-triazole, and benzimidazole. The results are indicated in Scheme 6.



**Scheme 6.** The utilization of  $\text{Cu}^{\text{I}}\text{-NHC}$  as a catalyst in Ullmann-type *N*-arylations.

The reactions were found to proceed with good to excellent yields (52–98%). The catalyst was also tested in the *N*-arylation reactions of heteroaryl chlorides with azoles. The hetero-coupling reaction of 2-chloroquinoline with imidazole, 1,2,3-triazole, and 4-phenylimidazole afforded excellent yields of 90–98%, and the reactions of 2-chloropyridine derivatives provided the coupling product with substantial yields of 80–95%, which confirmed that the  $\text{Cu}^{\text{I}}\text{-NHC}$  complex was an efficient catalyst. However, recycling data were not reported, and, therefore, the stability of the catalyst cannot be evaluated.

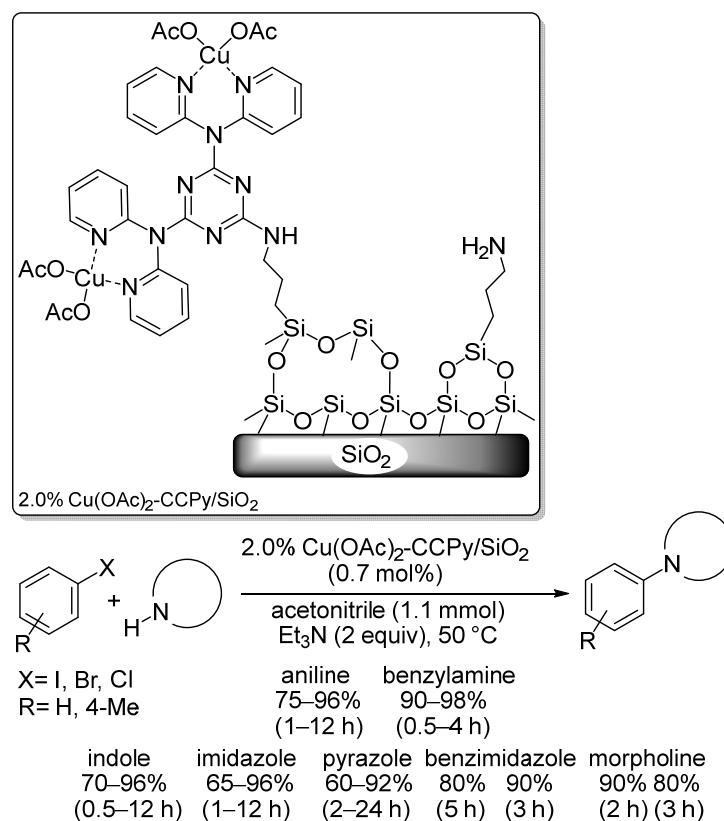
On account of their favorable properties, including high chemical, thermal, and hydrothermal stabilities and substantial surface areas, microporous organic polymers (MOPs) have been considered as suitable support materials for heterogeneous metal catalysts. The application of hypercrosslinked polymers (HCPs), also regarded as low-cost MOPs, proved to be particularly beneficial, as various metal complexes can be installed in their frameworks without further chemical modification. Moreover, the permanent porosity of HCPs, originating from an extensive chemical cross-linkage, was found to prevent the collapse of the polymer chains, resulting in the formation of a nonporous state [49–51]. The immobilization of an NHC-copper complex on hypercrosslinked polymers (HCPs) via an external cross-linking reaction was reported by Tan and Gu et al. [52]. HCP-NHC was prepared from *N,N*-dibenzylbenzimidazolium chloride and benzene, by using  $\text{FeCl}_3$  as a catalyst [53].  $\text{Cu-HCP-NHC}$  was synthesized at room temperature under a nitrogen atmosphere by stirring the mixture of HCP-NHC,  $\text{CuCl}$ , and sodium-*tert*-butoxide in tetrahydrofuran (THF) for 24 h. The Cu loading of the product was 7.78 wt%.  $\text{N}_2$  sorption studies of  $\text{Cu-HCP-NHC}$  revealed that a substantial amount of micropores were formed, together with some meso- and macropores. XPS patterns displayed Cu 2p signals at 933.8–934.0 eV, indicating the predominance of  $\text{Cu}^{\text{II}}$  species. The catalytic investigation of the sample was performed in the Ullmann-type C–N coupling of 4-iodoanisole and indole at 120 °C for 10 h by using 0.53 mol% of catalyst, DMSO as a solvent, and 2 equiv of  $\text{K}_2\text{CO}_3$  as a base. The isolated yield for the coupling product was 93% and 91% for the first and second applications of the catalyst, respectively. Further recycling studies were not reported, and hence the stability of the catalyst was not confirmed.



The functionalization of mesoporous materials (e.g., silica and alumina), with ionic liquids (ILs), providing the combination of textural properties with a tunable chemical environment, has been found to be a promising alternative for the preparation of supported metal catalysts [54]. Alves-Fernandes and Abarca et al. introduced a novel synthesis method for the generation of Cu nanoparticles immobilized on triazolium-based ionic liquids, and grafted on the surface of silica [55]. Different support materials were fabricated by anchoring various triazolium moieties on a silica matrix. The 1,4-disubstituted 1,2,3-triazoles were prepared by the click reaction of an alkyne and an azide, obtained in situ, by using  $[\text{CuI}(\text{PPh}_3)_3]$  as a catalyst. A support material with a high electron density (SIL1) was obtained via the addition of phenyl and benzyl groups to the triazolium ring, and other supports with lower electronic densities (SIL2 and SIL3) were also generated by applying alkyl chains instead of aromatic groups. Three samples were synthesized by mixing different triazoles with  $\text{SiO}_2$ , suspended in acetonitrile, followed by the addition of  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  in methanol and reduction by  $\text{NaBH}_4$ , which resulted in the formation of Cu nanoparticles immobilized on the surface of the support materials. The Cu loadings were 2.6%, 3.1%, and 2.8% for Cu/SIL1, Cu/SIL2, and Cu/SIL3, respectively. Structural characterization of the samples was performed by  $\text{N}_2$  sorption, FT-IR, and field emission scanning electron microscopy (FE-SEM). XPS spectra indicated the formation of mixed valence states of  $\text{Cu}^0$  and  $\text{Cu}^{\text{I}}$  for all samples, which was also confirmed by XRD patterns. STEM analysis revealed the (111) lattice fringes of Cu nanoparticles associated with the face-centered cubic (fcc) crystalline phase of  $\text{Cu}_2\text{O}$ . The predominance of the  $\text{Cu}^{\text{I}}$  species was also established by linear mixed model (LMM) analysis. The catalytic activities of the samples were investigated in the Ullmann-type C–N heterocoupling reactions of haloarenes with aniline, performed in DMSO at  $100^\circ\text{C}$  for 4 h, by using 1 mol% of catalyst and KOH as a base. The highest conversion (88%), product selectivity (95%), and turnover frequency ( $374\text{ h}^{-1}$ ) were obtained for the reaction of iodobenzene, in the presence of the Cu/SIL1, which proved to be the most active catalyst for all reactants. The transformations of chlorobenzenes afforded conversions of 44%, 31%, and 30% for Cu/SIL1, Cu/SIL2, and Cu/SIL3, respectively. Computational studies indicated a strong interaction between the SIL1 support and the Cu nanoparticles, which was assigned to a charge transfer between the ionic liquid and the Cu particles. It was suggested by the authors that the ionic liquid cation of SIL1 acted as an electron-like reservoir and modified the electronic environment of the active Cu particles by increasing the  $\text{Cu}^{\text{I}}/\text{Cu}^{\text{III}}$  ratio, which contributed to the enhanced catalytic activity of Cu/SIL1. However, the stability of the catalyst cannot be evaluated, as recycling data were not provided.

Another study for the preparation of a heterogeneous  $\text{Cu}^{\text{II}}$  nanocatalyst has been reported by Hemmati et al. The synthesis procedure was based on the functionalization of silica by melamine-bearing pyridine groups, working as the capping agents of catalytically active  $\text{Cu}^{\text{II}}$  species [56]. In the first synthesis step, a mixture of  $\text{SiO}_2$  and aminopropyltrimethoxysilane (APTMS) was heated under reflux conditions in toluene for 24 h. After purification, the product was dispersed in THF, followed by the addition of diisopropylethylamine and cyanuric chloride (CC). The resulting solid was treated with diisopropylethylamine in acetonitrile, and then dipyridylamine was added, and the mixture was treated at reflux temperature for 12 h. In this way, a solid material containing dipyridylamine moieties attached to triazine-functionalized silica was obtained, which was used as a support material of  $\text{Cu}(\text{OAc})_2$ . Immobilization of the precursor was accomplished from an aqueous solution under stirring at room temperature for 24 h. The Cu loading of the product, denoted as  $\text{Cu}(\text{OAc})_2\text{-CCPy}/\text{SiO}_2$ , was  $0.32\text{ mmol g}^{-1}$ . FTIR spectra confirmed that the functionalization of  $\text{SiO}_2$  by aminopropyl and melamine-bearing pyridine groups actually took place. Nitrogen sorption measurements indicated that the product had a microporous structure, and TEM images displayed silica nanoparticles of 10–15 nm, suggesting that the morphology of the silica support was retained after functionalization. SEM images also indicated the occurrence of aggregated particles. The  $\text{Cu}(\text{OAc})_2\text{-CCPy}/\text{SiO}_2$  sample was tested as a catalyst in the Ullmann heterocoupling reactions of amines with

aryl halides under aerobic conditions. The reactions were performed at 50 °C, by using 0.7 mol% of catalyst, acetonitrile as a solvent, and trimethylamine as a base. The results displayed in Scheme 7 also demonstrate the structure of the catalyst.

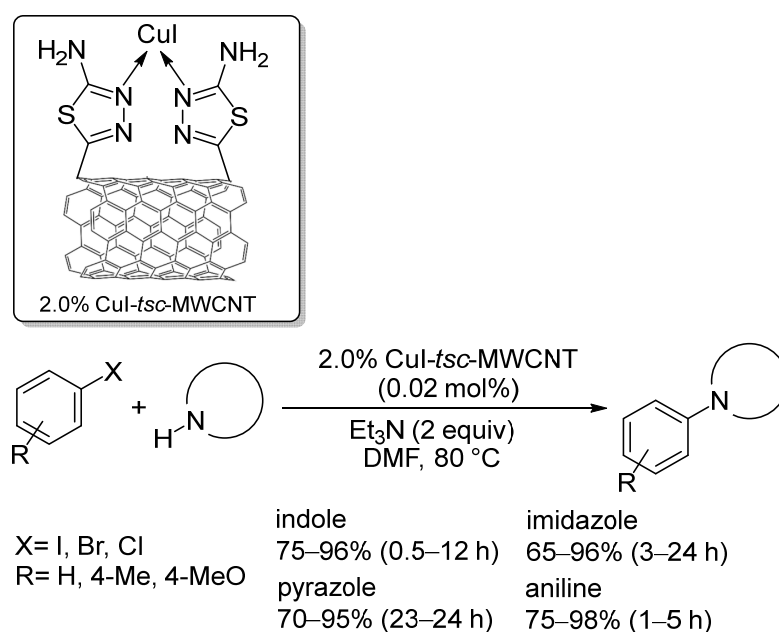


**Scheme 7.** C–N heterocoupling reactions catalyzed by 2.0% Cu(OAc)<sub>2</sub>-CCPy/SiO<sub>2</sub>.

The highest product yields of 90–96% were obtained for the transformations of iodobenzenes, proceeding for 0.5–2 h. For the reactions of bromo and chloro derivatives, similar yields could only be achieved by applying prolonged treatments of 0.5–4 h and 4–24 h, respectively. Recycling studies, effected for the reaction of bromobenzene and indole, gave evidence that no appreciable deactivation of the catalyst occurred up to five repeated applications (yield: 96–93%, avg. 94.8%, six runs). Hot filtration experiments also indicated that leaching of the active Cu<sup>II</sup> species did not take place, and, therefore, the Cu/CCPy/SiO<sub>2</sub> sample was considered a heterogeneous catalyst.

Another approach for the synthesis of heterogeneous copper catalysts was based on the immobilization of CuI on thiosemicarbazide (*tsc*) modified multi-walled carbon nanotubes (MWCNTs) [57]. In the synthesis procedure, a DMF solution of CuI was added to an as-prepared DMF dispersion of *tsc*/MWCNT [58], followed by stirring at room temperature for 24 h. After purification and drying, a solid product, denoted as CuI-*tsc*/MWCNT, was obtained, for which the Cu loading was 0.32 mmol g<sup>-1</sup>. The formation of *tsc*/MWCNT was confirmed by Raman and wavelength-dispersive X-ray (WDX) spectra. Energy dispersive spectra (EDS) indicated that CuI was successfully immobilized on the surface of the support material, whereas the covalent attachment of thiosemicarbazide moieties to MWCNT was established by TEM images. The catalytic test reactions were the *N*-arylations of indole, aniline, imidazole, and pyrazole, performed by various aryl halides, as shown in Scheme 8.

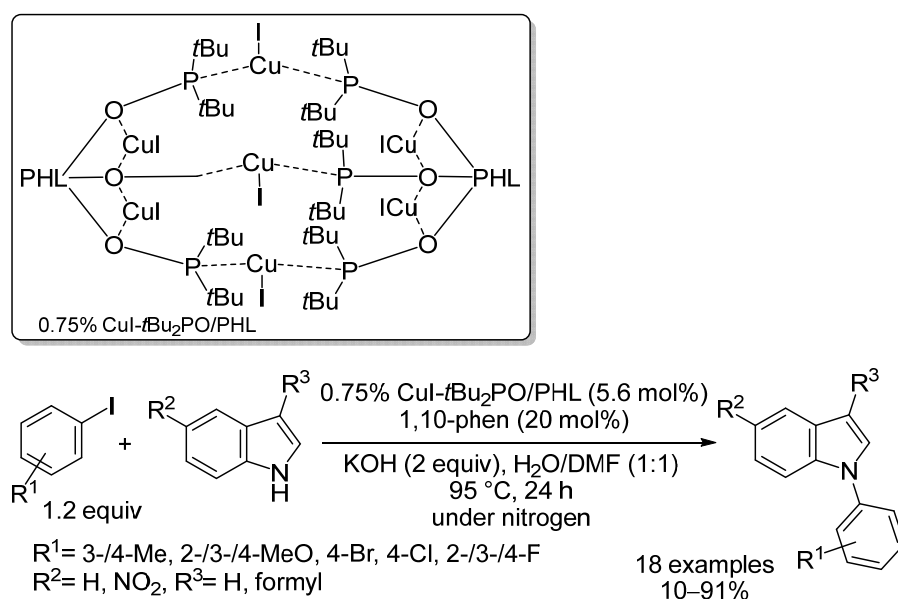




**Scheme 8.** Ullmann-type heterocoupling reactions catalyzed by CuI-*tsc*/MWCNT.

It was established that the CuI-*tsc*/MWCNT sample was an efficient catalyst for the heterocoupling reactions of aryl iodides and bromides, whereas the transformations of aryl chlorides provided lower yields, even at prolonged reaction times. A hot filtration test confirmed the absence of CuI leaching under reaction conditions, which referred to the heterogeneous nature of the catalyst. Recycling studies were carried out for the reaction of iodobenzene and indole, and only a minor decrease of activity was experienced (yield: 96–82%, avg. 92%, six runs), which indicated satisfactory catalyst stability.

Lignin, a natural, three-dimensional amorphous polymer containing a large number of phenolic hydroxyl, carboxyl, and carbonyl groups, has been recently recognized as a favorable support material of heterogeneous metal catalysts [59,60]. The unique physico-chemical properties of lignin make it suitable for the immobilization of metal complexes, which have been utilized in various catalytic transformations, including C–C coupling and cross-coupling reactions [61–64]. In a current study, Chen, Pen, and coworkers reported the synthesis and catalytic application of a lignin-supported copper complex in Ullmann-type *N*-arylation reactions [65]. Polyhydroxylated lignin (PHL) was obtained by dissolving demethylated lignin in an aqueous NaOH solution, followed by the addition of Fe(OH)<sub>3</sub> and hydrogen peroxide, and stirring at 60 °C for 60 min. PHL was modified via the addition of 4-dimethylaminopyridine (DMAP) and triethylamine (TEA) in THF and the subsequent treatment by di-*tert*-butylchlorophosphane (*t*Bu<sub>2</sub>PCl) at room temperature for 1 h, which resulted in the formation of phosphane-modified lignin, *t*Bu<sub>2</sub>PO/PHL. The immobilization of CuI on *t*Bu<sub>2</sub>PO/PHL was carried out under reflux conditions by using ethanol as a solvent. The final product, CuI-*t*Bu<sub>2</sub>PO/PHL, was subjected to structural characterization. FT-IR spectra showed that PHL was successfully modified with phosphane groups, and the incorporation of CuI was confirmed by EDS and XRD studies. N<sub>2</sub> sorption measurements revealed that CuI-*t*Bu<sub>2</sub>PO/PHL had a mesoporous structure with a pore diameter of 2.5–4 nm and a low specific surface area of 0.795 m<sup>2</sup>g<sup>−1</sup>. XPS spectra displayed two characteristic peaks at 933.9 eV and 953.7 eV, associated with the Cu 2p<sub>3/2</sub> and Cu 2p<sub>1/2</sub> signals, indicating the predominance of Cu<sup>I</sup>. The CuI-*t*Bu<sub>2</sub>PO/PHL sample was tested as a catalyst in the Ullmann heterocoupling reactions of indoles with aryl halides, as displayed in Scheme 9.



**Scheme 9.** *N*-Arylations promoted by CuI-*t*Bu<sub>2</sub>PO/PHL.

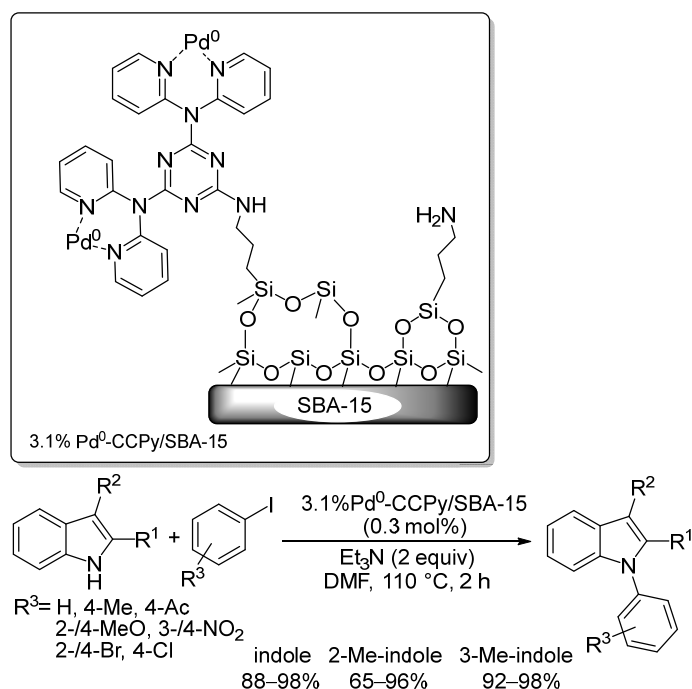
It was found that the reactions of 5-nitroindole with monosubstituted iodobenzenes bearing either electron donating groups (EDGs) or electron-withdrawing groups (EWGs) afforded the coupling products with moderate to good yields. On the other hand, the transformations of iodobenzene with substituted indoles proceeded with higher yields for the EWG-containing reactants. Recycling of the catalyst, investigated for the coupling reaction of iodobenzene with 5-nitroindole, revealed a significant activity decrease (yield: 85–28%, avg. 55%, five runs). The low stability of the catalyst was attributed to excessive copper leaching (the Cu content of CuI-*t*Bu<sub>2</sub>PO/PHL decreased from 0.557 to 0.0132 mmol g<sup>-1</sup> by the fifth cycle), together with fundamental structural changes, as revealed by SEM images.

## 2.2. Pd-Based Catalysts

There are only a few recent examples discussing Ullmann-type C–N heterocoupling reactions promoted by heterogeneous Pd catalysts. The *N*-arylations of indoles were investigated by using catalytically active melamine–pyridine functionalized SBA-15-supported Pd<sup>0</sup> nanoparticles by Veisi et al. [66]. The catalyst was prepared via anchoring of melamine-containing pyridine groups on SBA-15, followed by the generation of Pd nanoparticles. SBA-15 was synthesized from tetraethylorthosilicate (TEOS), by using Pluronic P123 triblock polymer as a template. Treatment of the aminopropyl-functionalized SBA-15 by cyanuric chloride and dipyridylamine resulted in the formation of dipyridylamine moieties on the surface of triazine-functionalized SBA-15, working as anchoring sites for the precursor PdCl<sub>2</sub>, which was subsequently reduced by hydrazine hydrate. The Pd loading of the final product, denoted as Pd<sup>0</sup>-CCPy/SBA-15, was 0.29 mmol g<sup>-1</sup> from ICP analysis. The sample was characterized by FT-IR spectroscopy and N<sub>2</sub> sorption measurements, and the formation of metallic Pd<sup>0</sup> species on the surface of SBA-15 was confirmed by XRD patterns, EDX analysis, and TEM images [67]. The Pd<sup>0</sup>-CCPy/SBA-15 sample displayed a pronounced catalytic activity in the Suzuki reactions of aryl halides with phenylboronic acid, and therefore it was also applied for the *N*-arylations of indoles under mild conditions.

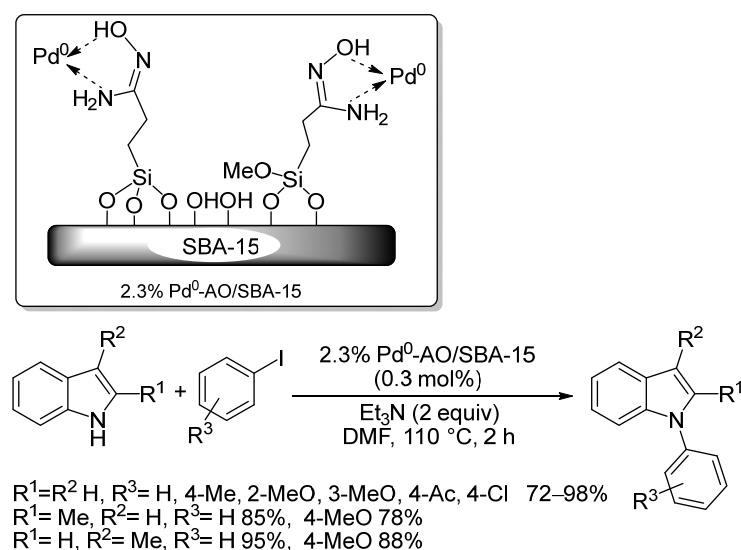
The results shown in Scheme 10 indicated that all the substituted iodobenzenes afforded the coupling products with high yields. It was found that 2-methylindole was less active than indole and 3-methylindole, which was attributed to steric effects. The absence of the C-arylation of indole was also pointed out. A recycling test, accomplished for the heterocoupling of iodobenzene and indole, gave evidence that the catalyst could be efficiently reused up to six times, with only a minor extent of deactivation (yield: 98–95%,

avg. 97%, seven runs). A hot filtration test also confirmed that the reactions proceeded in the heterogeneous phase.



**Scheme 10.** Ullmann heterocoupling reactions catalyzed by 3.1% Pd<sup>0</sup>-CCPy/SBA-15.

The preparation and application of another SBA-15-supported Pd<sup>0</sup> catalyst has been reported in a related study. In this case, 2-cyanoethyl-functionalized SBA-15 was treated with an aqueous solution of hydroxylamine, resulting in the formation of amidoxime (AO) groups utilized as anchoring species for the immobilization of PdCl<sub>2</sub>. The precursor was subsequently reduced by hydrazine hydrate [68]. SEM images revealed a rod-like morphology of the product, Pd<sup>0</sup>-AO/SBA-15, and TEM images indicated the formation of Pd<sup>0</sup> nanoparticles. For the catalytic investigation of Pd<sup>0</sup>-AO/SBA-15, the *N*-arylations of indoles with substituted aryl iodides were applied as model reactions. The results obtained for the heterocoupling reactions are summarized in Scheme 11.

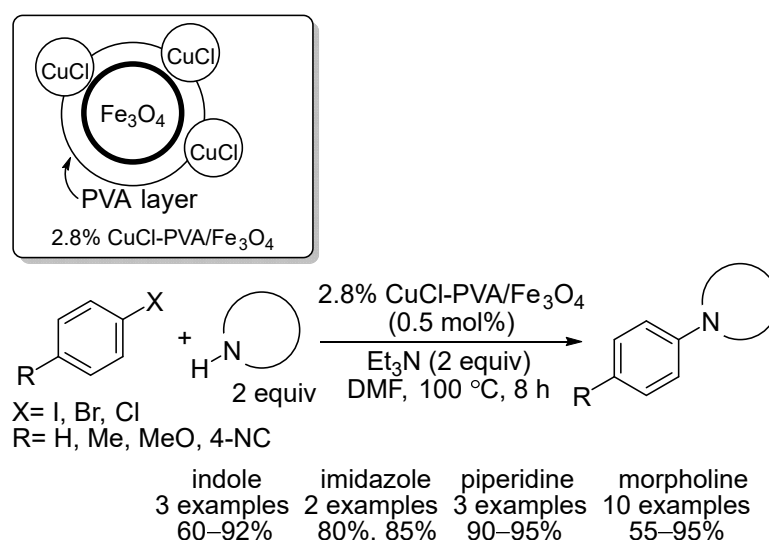


**Scheme 11.** Synthesis of *N*-arylindoles, catalyzed by Pd<sup>0</sup>-AO/SBA-15.

The reactions afforded the coupling products with high yields and proved to be selective for the *N*-arylated product, as the *C*-arylation of indole was not observed. A hot filtration test, accomplished for the *N*-arylation of indole with iodobenzene, revealed that after the removal of the catalyst from the reaction mixture, no further reaction took place, indicating that the Pd<sup>0</sup>-AO/SBA-15 sample was a heterogeneous catalyst. The sample also displayed good stability, as revealed by the minor decline of activity experienced in consecutive cycles (yield: 98–96%, avg. 97.3%, five runs).

### 2.3. Magnetic Catalysts

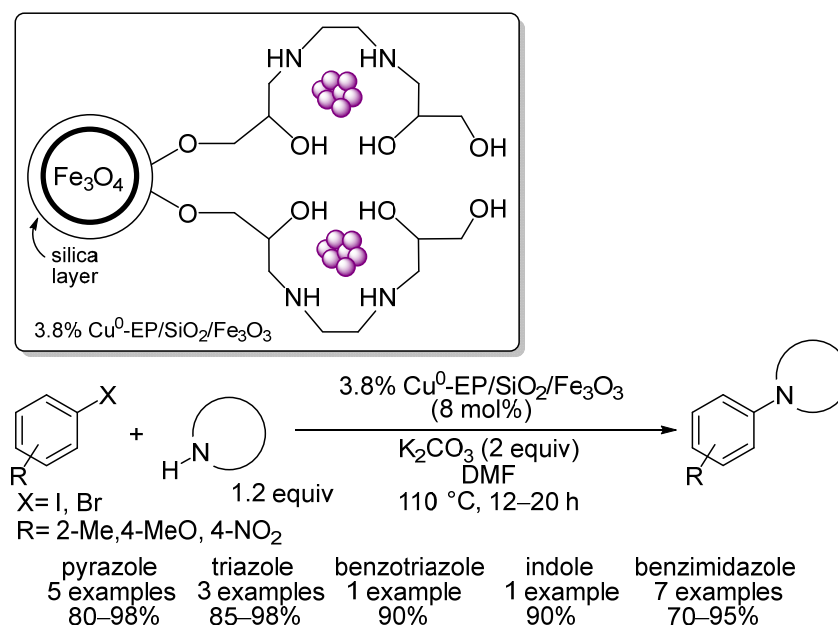
Heterogeneous catalysts containing magnetite (Fe<sub>3</sub>O<sub>4</sub>) nanoparticles have been the subject of considerable attention because of their low cost, enhanced stability, large surface area, low toxicity, and good biocompatibility. More importantly, these catalysts can be readily removed from the reaction mixtures with an external magnet, which considerably improves their recyclability [69–72]. In a recent study, Yousefi et al. reported results obtained for the catalytic application of Cu<sup>I</sup> species immobilized on polyvinyl-alcohol (PVA) coated magnetic Fe<sub>3</sub>O<sub>4</sub> nanoparticles in Ullmann-type *N*-arylations [73]. In the first step of the synthesis procedure, an aqueous dispersion of as-prepared Fe<sub>3</sub>O<sub>4</sub> nanoparticles [74] was subjected to ultrasonic treatment, followed by the addition of PVA, and then the reaction mixture was left under stirring for 24 h at 80 °C. The resulting solid, PVA/Fe<sub>3</sub>O<sub>4</sub>, was impregnated with an aqueous solution of CuCl at room temperature for another 24 h, which afforded the product, CuCl-PVA/Fe<sub>3</sub>O<sub>4</sub>, with a copper loading of 0.44 mmol g<sup>-1</sup>. Structural characterization of the sample was performed by FT-IR spectroscopy, field emission scanning electron microscopy (FESEM), EDX, vibrating sample magnetometry (VSM), ICP, XRD, and TEM. According to XRD patterns, the crystalline phase of Fe<sub>3</sub>O<sub>4</sub> was unaffected by the PVA coating, and FT-IR spectra indicated that the interaction of PVA with the magnetic nanoparticles took place via the surface hydroxyl groups. FESEM images revealed the formation of quasi-spherical Fe<sub>3</sub>O<sub>4</sub> nanoparticles with a mean diameter of 10–20 nm, and EDX spectra confirmed that efficient coordination of the copper ions on the Fe<sub>3</sub>O<sub>4</sub>-PVA surface took place. The characteristic signals of the Cu<sup>I</sup> species also appeared on the XPS spectra at the binding energies 932.3 and 952.2 eV, assigned to the Cu 2p<sub>3/2</sub> and Cu 2p<sub>1/2</sub> signals, respectively. The sample was tested as a catalyst in the C–N heterocoupling reactions of various heterocyclic amines with aryl halides. The results are indicated in Scheme 12.



**Scheme 12.** Ullmann heterocoupling reactions catalyzed by CuCl-PVA/Fe<sub>3</sub>O<sub>4</sub>.

For the reactions of iodo- and bromobenzenes, high product yields were obtained, irrespective of the electron donating or withdrawing character of their substituent. On the other hand, the transformations of chlorobenzenes afforded considerably lower yields of 55–60%. Recycling of the catalyst was investigated for the reaction of bromobenzene and morpholine. After completing the reaction, the catalyst was removed by an external magnet and reused. It was established that the catalyst remained efficient up to seven cycles (yield: 95–86%, avg. 91.6%, eight runs), and a hot filtration test confirmed that the CuCl-PVA/Fe<sub>3</sub>O<sub>4</sub> sample may be considered a heterogeneous catalyst.

Eshghi et al. synthesized magnetic Cu nanorods and investigated their catalytic performance in the Ullmann heterocoupling reaction [75]. Magnetic Fe<sub>3</sub>O<sub>4</sub> particles, prepared by co-precipitation, were covered by a silica layer by applying the Stöber sol-gel method [76]. The resulting solid, SiO<sub>2</sub>/Fe<sub>3</sub>O<sub>4</sub>, was added to an ethanol solution of epibromohydrin (EP), and the mixture was subsequently stirred at 60 °C for 5 h. The dry precipitate was suspended in ethylenediamine (EN), followed by stirring at 60 °C for another 24 h. Further treatment of the product with another portion of epibromohydrin resulted in the formation of a solid material, EP/SiO<sub>2</sub>/Fe<sub>3</sub>O<sub>4</sub>, containing a polydentate ligand bonded on the surface hydroxyl groups of the silica-coated magnetic nanoparticles [77]. This was applied as the support material of Cu nanorods, produced from the ethanol solution of the precursor Cu(OAc)<sub>2</sub> under reflux conditions, followed by reduction with NaBH<sub>4</sub>. The final product, Cu<sup>0</sup>-EP/SiO<sub>2</sub>/Fe<sub>3</sub>O<sub>4</sub>, was subjected to structural characterization. XRD patterns indicated that the crystal structure of Fe<sub>3</sub>O<sub>4</sub> was retained after modification. According to TGA curves, the amount of the organic linker on the surface of the magnetic nanoparticles was 0.6 mmol g<sup>-1</sup>. TEM images gave evidence that Cu nanorods of 10 nm were distributed on the surface of spherical SiO<sub>2</sub>/Fe<sub>3</sub>O<sub>4</sub> particles with an average diameter of 20 nm. The Cu loading of the product, 2.59 mmol g<sup>-1</sup>, was determined by ICP analysis. The catalytic test reactions, the *N*-arylations of various heterocycles with aryl halides, were performed by using 8 mol% of catalyst, K<sub>2</sub>CO<sub>3</sub> as a base, and DMF as a solvent. The results are displayed in Scheme 13.

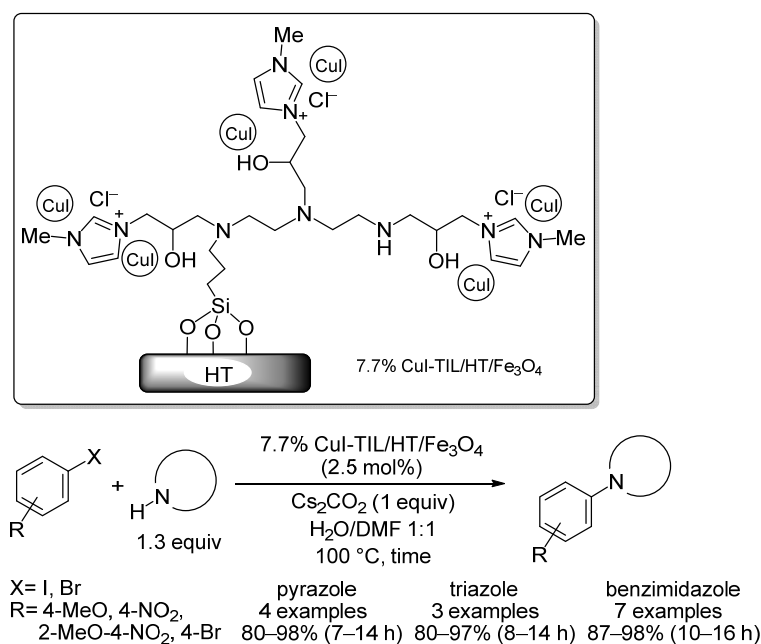


**Scheme 13.** *N*-Arylations of heterocycles, catalyzed by Cu<sup>0</sup>-EP/SiO<sub>2</sub>/Fe<sub>3</sub>O<sub>4</sub>.

For the reactions of various heterocycles, including benzimidazole, indole, pyrazole, and 1,2,4-triazole, substantial product yields were obtained by varying the reaction time between 12–20 h. A recycling test was accomplished for the *N*-arylation of pyrazole with 4-methoxyiodobenzene, and no appreciable deactivation was observed (yield: 98–90%, avg. 94%, five runs). The Cu loading of the recovered catalyst was 1.82 mmol g<sup>-1</sup> after the fifth

cycle, indicating a low amount of leaching, and TEM images confirmed that no structural modification of the catalyst occurred under reaction conditions.

The preparation and the catalytic application of a hydrotalcite-based magnetic CuI nanocatalyst have been recently reported by Rajabzadeh and Khalifeh et al. [78]. In the synthesis procedure, the surface of a magnetic hydrotalcite, HT/Fe<sub>3</sub>O<sub>4</sub>, was functionalized by 3-chloropropyltrimethoxysilane via covalent attachment, performed in toluene under reflux conditions [79]. The resulting solid was treated by a tricationic ionic linker (TIL) obtained from epichlorohydrine and 1-methylimidazole. This linker was dissolved in ethanol, and the reaction mixture was kept at boiling temperature under stirring for 24 h. The dispersion of the modified magnetic hydrotalcite, TIL/HT/Fe<sub>3</sub>O<sub>4</sub>, and CuI in acetonitrile was subsequently heated at 50 °C under an Ar atmosphere for 8 h, which afforded the final product, 7.7 wt% CuI-TIL/HT/Fe<sub>3</sub>O<sub>4</sub>. The anchoring of TIL on the surface of the magnetic support material was revealed by FT-IR spectra. XRD analysis indicated the formation of Fe<sub>3</sub>O<sub>4</sub> nanoparticles on the surface of hydrotalcite, and the presence of Cu<sup>I</sup> in CuI-TIL/HT/Fe<sub>3</sub>O<sub>4</sub> was also confirmed. According to FESEM and TEM images, the plate-like morphology of HT/Fe<sub>3</sub>O<sub>4</sub> was maintained after functionalization and the immobilization of CuI. The catalytic properties of CuI-TIL/HT/Fe<sub>3</sub>O<sub>4</sub> were investigated in the *N*-arylations of various heterocycles with aryl halides, and the results are shown in Scheme 14.



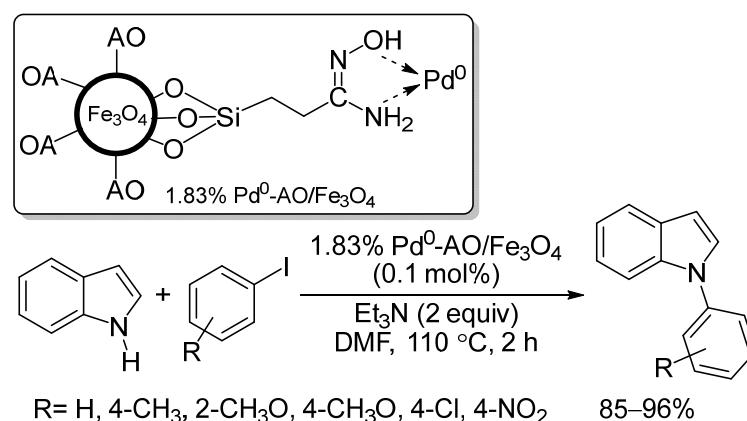
**Scheme 14.** Heterocoupling reactions of *N*-heterocycles with aryl halides, promoted by CuI-TIL/HT/Fe<sub>3</sub>O<sub>4</sub>.

The coupling products were formed with good yields, and the transformations of aryl halides containing both Br and I substituents were found to be selective for the C–I bond. Recycling studies performed for the reaction of *p*-methoxyiodobenzene with benzimidazole gave evidence that the catalyst could be used in six consecutive cycles without an appreciable decrease of activity (yield: 97–92%, avg. 95.8%, six runs). A hot filtration test also indicated the heterogeneous nature of the catalyst.

The preparation and the catalytic application of a magnetically recoverable Pd nanocatalyst have been reported by Ghorbani-Vaghei et al. [80]. The synthesis procedure was based on the production of amidoxime-functionalized Fe<sub>3</sub>O<sub>4</sub> particles, which were applied as the support material of the active Pd species. Magnetic Fe<sub>3</sub>O<sub>4</sub> nanoparticles were obtained by chemical co-precipitation of Fe<sup>III</sup> and Fe<sup>II</sup> ions, followed by the addition of NH<sub>4</sub>OH, which resulted in the formation of surface hydroxyl groups [81]. After dispersing the Fe<sub>3</sub>O<sub>4</sub>



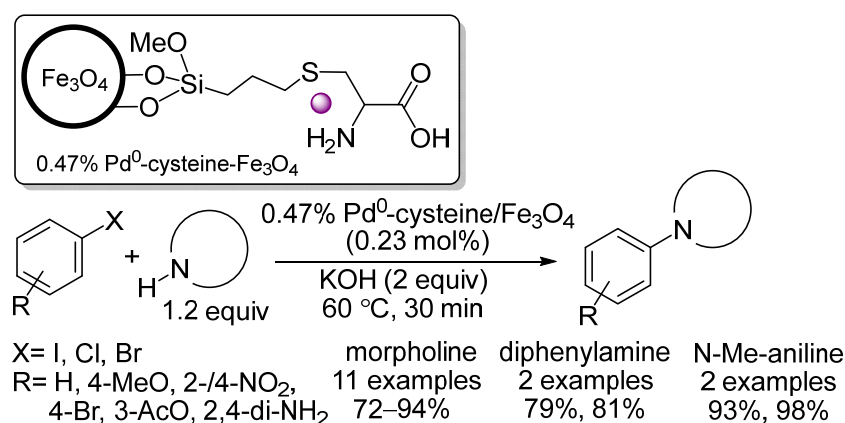
powder in toluene, triethoxyethylcyanide was added, and the reaction was completed at 100 °C for 48 h under an argon atmosphere. Subsequent treatment with an aqueous hydroxylamine solution produced amidoxime (AO) groups on the surface of the magnetic nanoparticles. The resulting solid (AO/Fe<sub>3</sub>O<sub>4</sub>) was dispersed in acetonitrile, followed by the addition of PdCl<sub>2</sub> and stirring at room temperature for 10 h and the subsequent reduction of the precursor with hydrazine hydrate. The final product, Pd<sup>0</sup>-AO/Fe<sub>3</sub>O<sub>4</sub>, had a Pd loading of 1.83 wt%, obtained from ICP-AES and EDS. FESEM and TEM images revealed spherical morphologies for both the functionalized Fe<sub>3</sub>O<sub>4</sub> and the Pd nanoparticles, for which the mean diameters were 10–15 and 3 nm, respectively. The catalytic performance of the Pd<sup>0</sup>-AO/Fe<sub>3</sub>O<sub>4</sub> sample was investigated in the Ullmann-type *N*-arylations of indoles with iodobenzenes by using 0.1 mol% catalyst, triethylamine as a base and DMF as a solvent. The results are summarized in Scheme 15.



**Scheme 15.** *N*-Arylations catalyzed by 1.83% Pd<sup>0</sup>-AO/Fe<sub>3</sub>O<sub>4</sub>.

The coupling reaction proved to be selective for the formation of the *N*-aryl-substituted product and proceeded with excellent yields for aryl iodides containing both electron-donating and electron-withdrawing substituents. Recycling of the Pd<sup>0</sup>-AO/Fe<sub>3</sub>O<sub>4</sub> catalyst revealed satisfactory stability (yield: 96–82%, avg. 90%, seven runs). However, it should be noted that these data were obtained for the Suzuki reaction of 4-methyl iodobenzene with phenylboronic acid, and no related data were disclosed for the *N*-arylations.

Another recyclable magnetic Pd nanocatalyst has been fabricated by Hajipour et al. [82]. The magnetic Fe<sub>3</sub>O<sub>4</sub> nanoparticles, prepared by co-precipitation [80], were coated with a silica layer upon reaction with tetraethyl orthosilicate (TEOS). In the next step, 3-iodopropyltrimethoxysilane was added in a nitrogen atmosphere to the Fe<sub>3</sub>O<sub>4</sub>/SiO<sub>2</sub> material, dispersed in toluene, and the mixture was heated under reflux conditions for 24 h. The following treatment of the product with cysteine and K<sub>2</sub>CO<sub>3</sub> was performed under similar conditions in acetonitrile. The formation of iodo-functionalized groups on the surface of the silica layer ensured the grafting of cysteine moieties on the magnetic nanoparticles. Finally, palladium acetate was immobilized on the magnetic support in ethanol, which resulted in the formation of the product, Pd<sup>0</sup>-cysteine/Fe<sub>3</sub>O<sub>4</sub>. ICP analysis revealed that the Pd loading of the sample was 0.47 wt%. Experimental evidence for the immobilization of cysteine moieties on the surface of the magnetic nanoparticles was obtained by FT-IR spectroscopy. XRD spectra displayed characteristic signals corresponding to the silica-coated magnetic nanoparticles and the Pd<sup>0</sup> species, whereas TEM images indicated the formation of monodispersed, spherical Pd nanoparticles with an average diameter of 14 nm. The catalytic activity of Pd<sup>0</sup>-cysteine/Fe<sub>3</sub>O<sub>4</sub> was examined in the *N*-arylations of aryl halides with various amines, and the coupling products were obtained with pronounced yields (Scheme 16).



**Scheme 16.** C–N heterocoupling reactions catalyzed by Pd<sup>0</sup>-cysteine/Fe<sub>3</sub>O<sub>4</sub>.

A heterogeneous pathway was confirmed by a hot filtration test, indicating that no further reaction progress took place after the removal of the magnetic Pd catalyst, which was in accordance with the result of ICP analysis, indicating that the amount of dissolved Pd was 0.03 ppm.

### 3. Conclusions

It may be ascertained that the Ullmann-type C–N heterocoupling reaction remained an efficient and versatile method for the synthesis of *N*-arylamines. Because of its importance in medicinal chemistry and in materials science, substantial efforts have been made for the development of novel and recyclable heterogeneous catalysts with improved performances. A variety of ligands have been applied for the surface modifications of the support materials utilized for the immobilization of the active metal species. The introduction of green procedures, including mild reaction temperatures, ligand-free conditions, the application of ionic liquids as modifiers, and the replacement of toxic organic compounds by environmentally friendly alternatives, has also gained increasing importance. Although copper-based catalysts have still been predominantly used for *N*-arylations, the efficiency of Pd catalysts has also been confirmed. Furthermore, the utilization of magnetic Fe<sub>3</sub>O<sub>4</sub> nanoparticles as support materials has been found to promote catalyst recovery and recycling to an appreciable extent. Nevertheless, in a few cases, insufficient information has been disclosed on the stabilities of the working catalysts. Considering the current limitations of Ullmann-type C–N heterocoupling reactions, further studies should be focused on the development of more efficient heterogeneous catalysts with low metal loadings and enhanced stabilities to be applied for an extended substrate scope under mild conditions. This would be a significant contribution to the prospective syntheses of pharmaceutically important molecules, which may also be suitable for large-scale applications.

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