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Recent achievements in copper catalysis for C-N bonds formation

Alexei D. Averin, Anton S. Abel, Olga K. Grigороva, Gennadij V. Latyshev, Yury N. Kotovshchikov, Alexander Yu. Mitrofanov, Alla Bessmertnykh-Lemeune, Irina P. Beletskaya*

Abstract: A mini-review describes the development of the catalysis by Cu(I) complexes aimed at the formation of C-N bonds at the Lomonosov MSU during 2010s. The main approach employs the amination of aryl and heteroaryl halides with the amines and polyamines, in this direction a great versatility of starting compounds was achieved: adamantane-containing amines, linear diamines, oxadiazines and polyamines, various aryl iodides and bromides, derivatives of pyridine and quinoline were used for this purpose. In more peculiar cases, the copper catalysis was used for steroids transformations, including vinylation of azoles, wide-spread “click” reactions for the conjugate syntheses, and successful heterogenization of the copper catalysts were also undertaken.

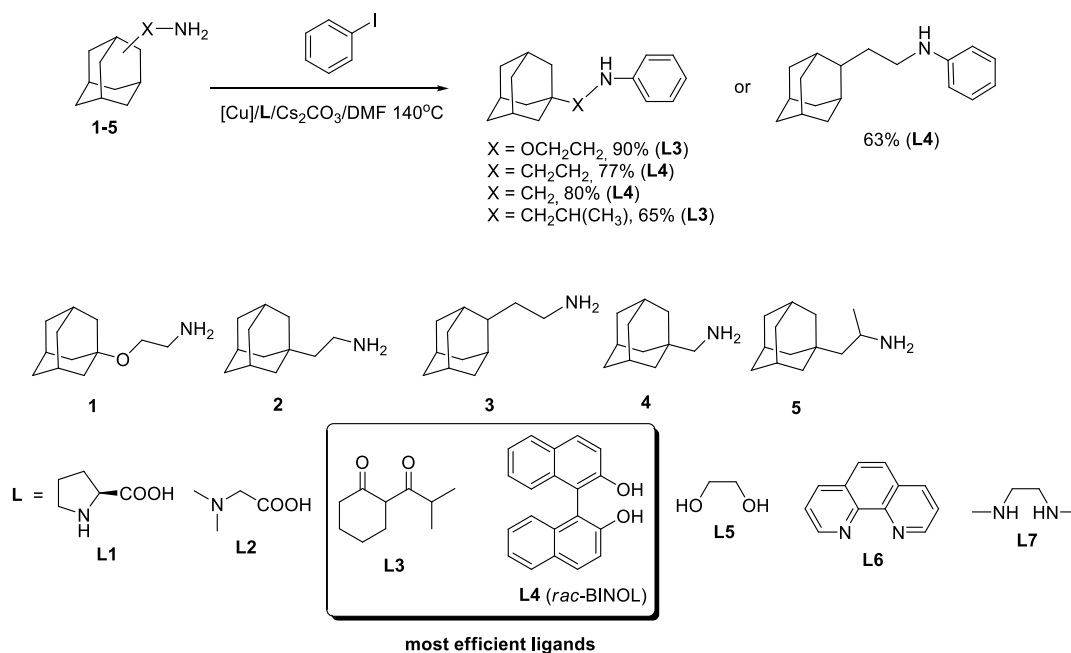
Keywords: Cu catalysis, amination, polyamines, adamantane, “click” reactions, steroids, immobilization

1 Introduction

The so-called renaissance of the Ullmann chemistry has become an important trend in the modern catalysis. The change of expensive palladium often associated with enough toxic phosphine ligands for a much cheaper copper boosted the search for new catalytic protocols in the formation of C–O, C–S and especially C–N bonds. The reviews covering the general aspects of the modern Ullmann chemistry are now abundant, they were published by Ma [1], Evano [2], Monnier [3], Jiang [4], Sambiasi [5], a special chapter to this topic is dedicated in the recent comprehensive handbook [6]. Among the principal investigations in the field of the copper-mediated amination [7-12] and amidation [13, 14] in last 15 years more specialized reviews can be cited [15, 16]. Our own interest in the copper-catalyzed reactions exceeds the frames of purely Ullmann reactions due to a wide scope of various catalytic transformations promote by this metal and cover the following aspects: formation of C(sp²)–P bonds [17-19], arylation with iodonium salts [20], formation of C–S and C–C bonds in the reactions with alkynes [21, 22], use of the chiral Cu(II) complexes in the asymmetric addition reactions catalyzed by optically active Lewis acids [23-26], application of the heterogeneous copper catalysts like copper nanoparticles (CuNPs) [27] and copper-containing MOFs [28]. Our attention was also drawn by the Cu(I)-catalyzed Sonogashira coupling [29, 30], formation of C–N bonds under the conditions of Chan-Lam-Evans reaction [31] or in the presence of poly(ethylene) glycols [32], the synthesis of polycyclic compounds [33]. As for reviews, the two approaches, via Pd- and Cu-catalyzed reactions in the C–N bond formation, were thoroughly compared in [34], while C–C and C–S bonds formation was overviewed in [35, 36].

In the present mini-review the material is focused properly on the C–N bond formation catalyzed by copper complexes and deals with the amination of (hetero)aryl halides and CuAAC (“click”) reactions applied for the conjugates syntheses. Historically we intensively studied the Pd(0)-catalyzed amination reactions with adamantane-containing amines [37-43] and linear polyamines [44-48]. Many efforts were done for the elaboration of the synthetic approaches to polyazamacrocycles [49-53]. In this connection, the outline of the possibilities of the copper-catalyzed amination will serve as a timely complement to the acquired knowledge on the palladium-mediated synthetic approaches.

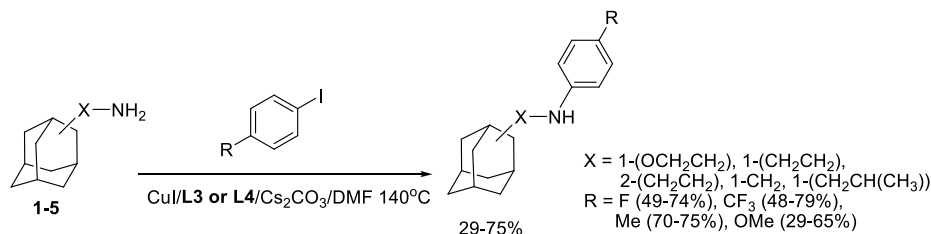
2 Cu(I)-catalyzed arylation of adamantane-containing amines



Scheme 1: Optimization of Cu-catalyzed arylation of adamantane-containing primary amine.

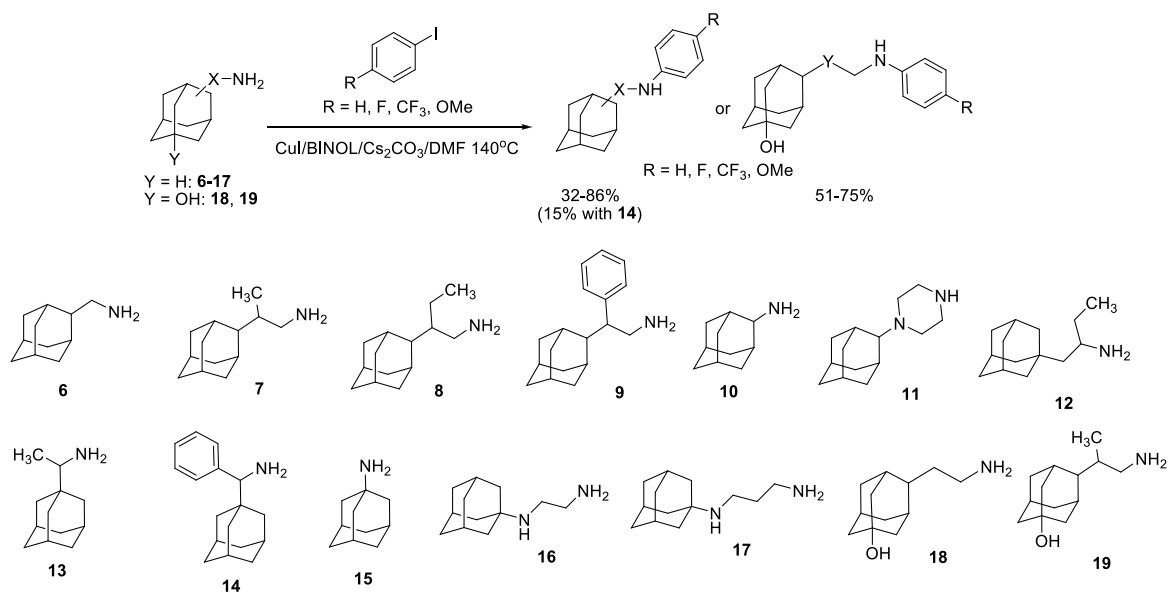
Our first goal was the search for the most efficient catalytic system for the arylation of the adamantane-containing amines [54]. In the preliminary experiments we chose five primary amines **1-5** differing by the spatial hindrances at the amino groups and introduced them in the arylation with iodobenzene in the presence of [Cu]/L catalytic systems in which the nature of the copper source and the ligand was varied (Scheme 1). Among various sources of copper (CuI, Cu₂O, CuO, CuOTf, CuOAc, CuBr•Me₂S) the best results were shown by a traditional copper iodide, and in some cases cuprous and cupric oxides could be also used. The employed ligands **L** were as follows: L-proline (**L1**), *N,N*-dimethyl glycine (**L2**) (*N,O*-ligands), 2-isobutyrylcyclohexanone (**L3**), *rac*-BINOL (**L4**), ethylene glycol (**L5**) (*O,O*-ligands), 1,10-phenanthroline (**L6**), *N,N*-dimethylethylenediamine (**L7**) (*N,N*-ligands). It was found out that **L3** and **L4** ligands provided the best yields of the arylation products. CuI/**L3** or CuI/**L4** catalytic systems were used further for the synthesis of various *N*-arylated derivatives of adamantyl-substituted primary amines. Cesium carbonate was always employed as a base and the reactions were run in DMF at 140°C with 0.5 M concentrations of the reagents.

The application of *para*-substituted iodobenzenes in the couplings with the same amines **1-5** showed that the substituent strongly influenced the products yields (Scheme 2). The best results were observed for the reactions with *p*-iodotoluene while the most problematic reagent was *p*-iodoanisole due to a strong electron-donor effect of the methoxy group.



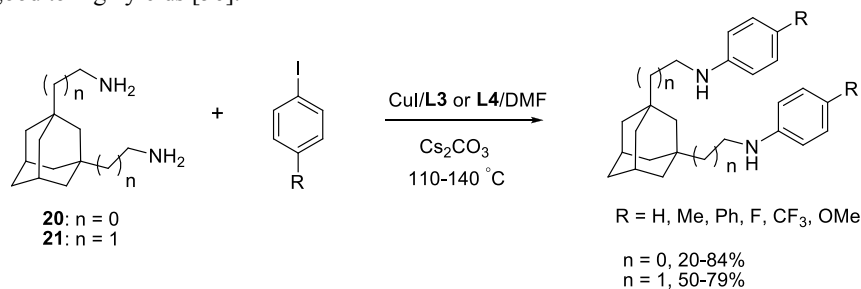
Scheme 2: Cu(I)-catalyzed arylation of the adamantane-containing amines with *para*-substituted iodobenzenes.

Further investigations englobed a series of the amines **6-19** with more structural varieties, in all reactions *rac*-BINOL (**L4**) was used as the ligand (Scheme 3). In the majority of cases the yields of the products of arylation with *para*-substituted iodobenzenes were from moderate to high attaining 70–86% in the case of less sterically demanding amines, the increase in the spatial hindrances (especially in **9**, **12**, **13**, **15**) led to a decrease in the yields of the target products, and amine **14** was found to be the most problematic [55].



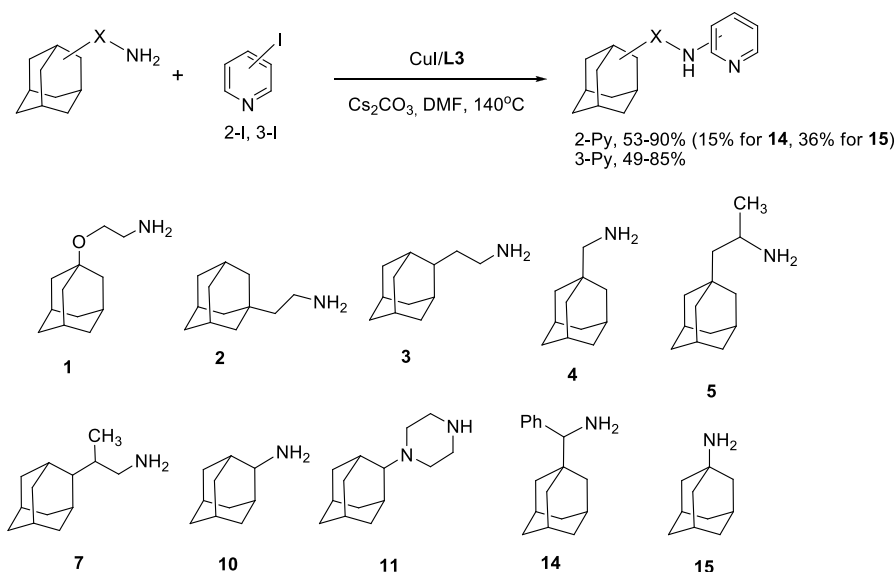
Scheme 3: Expanding the scope of adamantylated amines in the copper-catalyzed arylation reaction.

The method was successfully applied to adamantane-containing diamines **20** and **21** (Scheme 4). The reactions with the diamine **20** possessing the amino groups closer to the adamantane scaffold demonstrated greater dispersion of the yields and only **L4** was helpful for its *N,N'*-diarylation. Products of the monoarylation were also obtained in some cases (R = Me, CF₃, OMe). Diamine **21** was more reactive and both ligands, **L3** and **L4** allowed the synthesis of diarylated species in good to high yields [56].



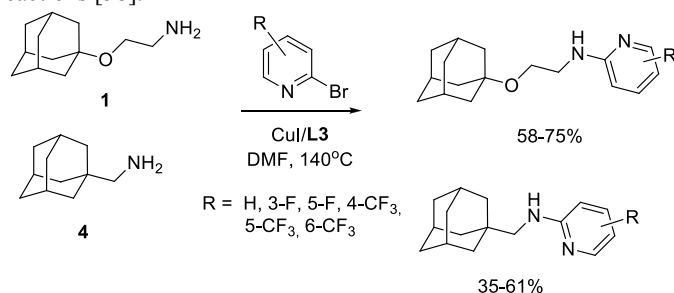
Scheme 4: Cu(I)-catalyzed arylation of the adamantane-containing diamines with *para*-substituted iodobenzenes.

3 Copper catalysis in the adamantane-containing amines heteroarylation



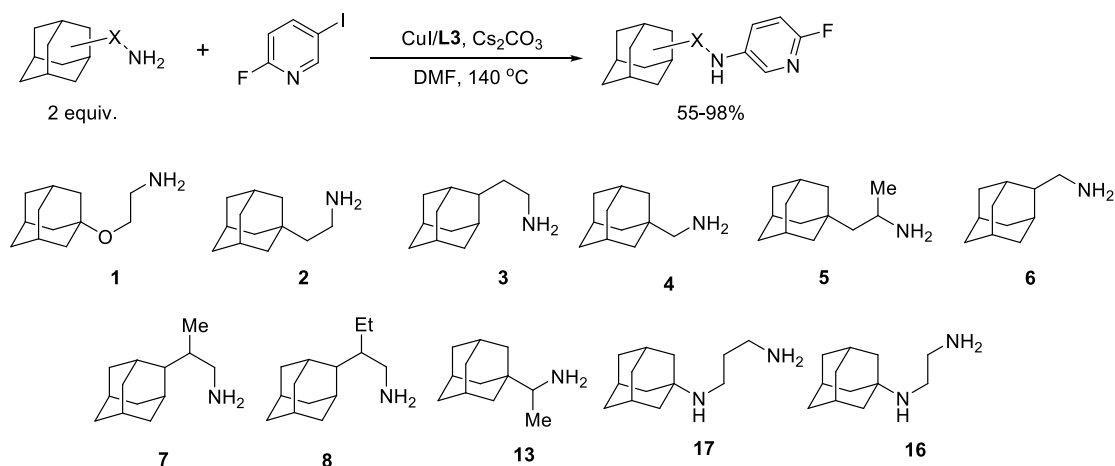
Scheme 5: Cu-catalyzed synthesis of *N*-pyridyl derivatives of adamantylated amines.

The heteroarylation of various adamantylated amines was explored using 2-iodo- and 3-iodopyridines (Scheme 5). Ligands **L1**–**L4** were tested in these reactions and only **L3** was found to be suitable for this purpose. 2-Iodopyridine was more reactive but the products were obtained in good yields for both isomeric halides. Nevertheless, when 2-iodopyridine was reacted with more sterically hindered amines such as **14** and **15**, the yields of the target products decreased up to 15 and 36%, respectively [57]. It was found that the reaction also smoothly proceeded with more available 2-bromopyridines bearing fluoro- and trifluoromethyl substituents at the pyridine ring (Scheme 6). The yields of the target products were higher in the case of the amine **1** than with **4** what is in a good correspondence with the closer position of the amino group to the adamantane core in the case of **4**. It was found possible to introduce sterically hindered 2-bromo-3-fluoropyridine in these reactions [58].



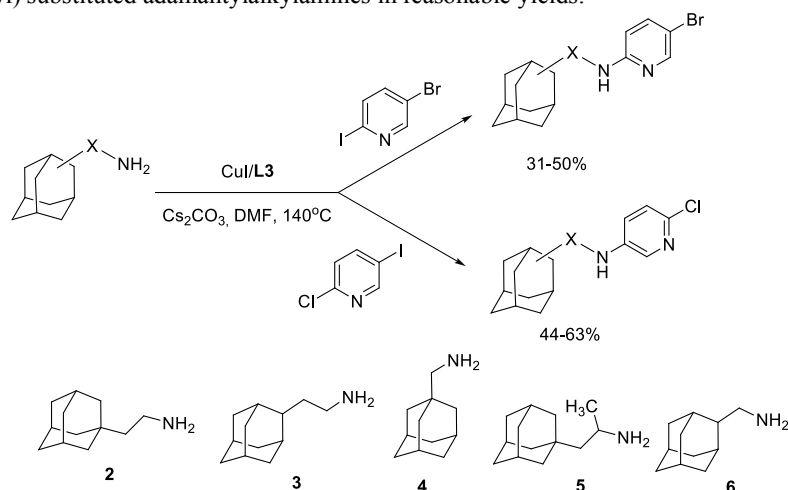
Scheme 6: 2-Bromopyridines with fluorine-containing substituents in Cu(I)-catalyzed heteroarylation.

A variety of amines **1**–**8**, **13**, **16** and **17** were studied in the copper-mediated amination of 2-fluoro-5-iodopyridine (Scheme 7). Not only the reaction products attracted out attention as those bearing aminofluoropyridine – a promising pharmacophore, but also the problem of the competition of the catalytic substitution of the iodine and non-catalytic substitution of the fluorine atom. In the case of the equimolar ratio of the starting compounds the yields of the products of the catalytic amination were enough low and substantial amounts of the 2-aminopyridine derivatives were formed. However, with the application of 2 equiv. of starting amines the results improved drastically allowing almost quantitative synthesis of the target 5-amino-2-fluoropyridines [59].

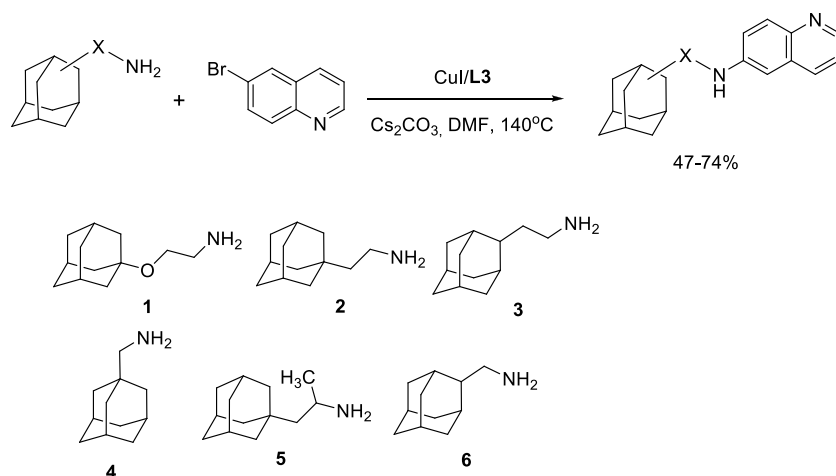


Scheme 7: Cu(I)-mediated heteroarylation of adamantane-containing amines with 2-fluoro-5-iodopyridine.

Following our investigations on the application of palladium catalysis for the amination of various dichloro-, di-bromo- and bromochloropyridines where the comparison with the Cu(I)-catalyzed amination of 2,5-dibromopyridine was done [60], we also demonstrated the possibilities of the copper-catalyzed amination with adamantylated amines with other dihalogenopyridines (Scheme 8). The same catalytic system was helpful for a selective substitution of the iodine atoms in 5-bromo-2-iodopyridine and 2-chloro-5-iodopyridine affording corresponding *N*-(5-bromopyridin-2-yl) and *N*-(2-chloropyridin-5-yl) substituted adamantylalkylamines in reasonable yields.



Scheme 8: Synthesis of *N*-(5-bromopyridin-2-yl) and *N*-(2-chloropyridin-5-yl)-substituted (adamantyl)alkylamines.

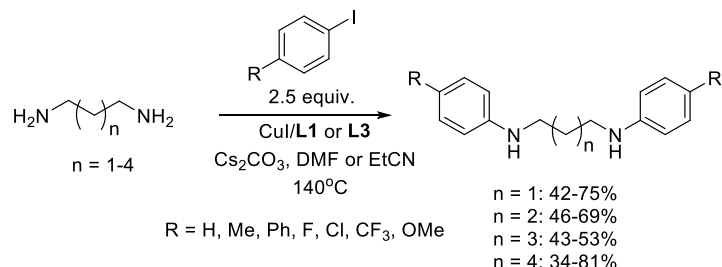


Scheme 9: Catalytic introduction of the quinoline substituent in the adamantylalkylamines.

Amines **1–6** were employed in the Cu(I)-catalyzed amination of another heterocyclic halide, i.e. 6-bromoquinoline (Scheme 9). The dependence of the reaction outcome on the steric hindrances at the amino group was enough clear, the best result (74% yield) was recorded in the case of the less sterically demanding amine **1**. The attempts to use 2- or 4-

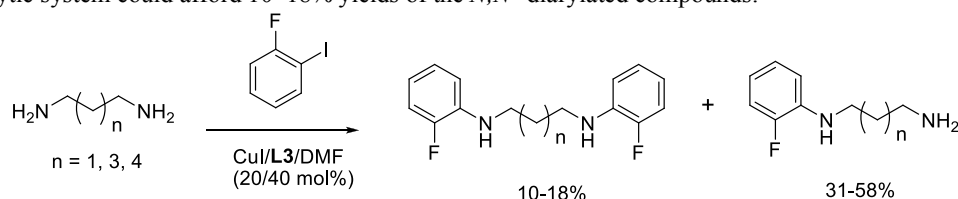
chloroquinolines in the same reaction were not as successful and the yields did not surpass 30% due to numerous side reactions.

4 *N,N'*-diarylation of di- and polyamines using Cu(I) catalysis



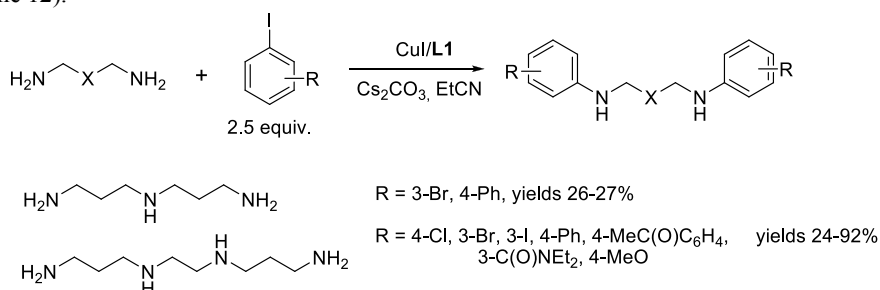
Scheme 10: Cu(I)-catalyzed *N,N'*-diarylation of the diamines.

Having acquired enough experience with the copper-catalyzed (hetero)arylation of monoamines, we thoroughly studied the possibilities of the *N,N'*-diarylation of di- and polyamines [61]. At first, a series of linear diamines was investigated which differ by the number of methylene groups between N atoms (Scheme 10). The reactions were run with different *para*-substituted iodobenzenes. Only ligands **L1** and **L3** were found to be suitable in these reactions, and **L1** was superior to **L3** in the reaction of ethylenediamine and pentane-1,5-diamine. In fact, for all these diamines the systems Cu/**L1**/PPh₃ or Cu/**L3**/PPh₃ provided the best yields of the diarylation products. The main by-products were the monoarylated derivatives, in some cases they were isolated as pure compounds. Such compounds became predominant in the reactions with the sterically hindered 2-fluoroiodobenzene (Scheme 11), and even the application of 20/40 mol% catalytic system could afford 10–18% yields of the *N,N'*-diarylated compounds.



Scheme 11: Arylation of linear diamines with 2-fluoroiodobenzene.

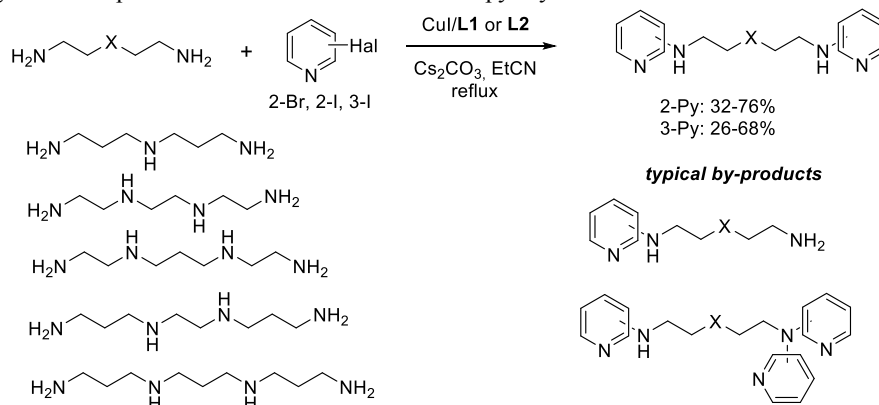
The introduction of the tri- and tetraamine in the similar reactions demonstrated that the Cu/**L1**/EtCN catalytic system was more efficient as it diminished the formation of the side products arising from the arylation of the secondary amino groups [62]. As a result, it was possible to introduce *para*- and *meta*-substituted iodobenzenes in the *N,N'*-diarylation process, though the product yields differed from low to high depending on the nature of the substituent in the aryl ring (Scheme 12).



Scheme 12: Cu(I)-catalyzed *N,N'*-diarylation of the tri- and tetraamines.

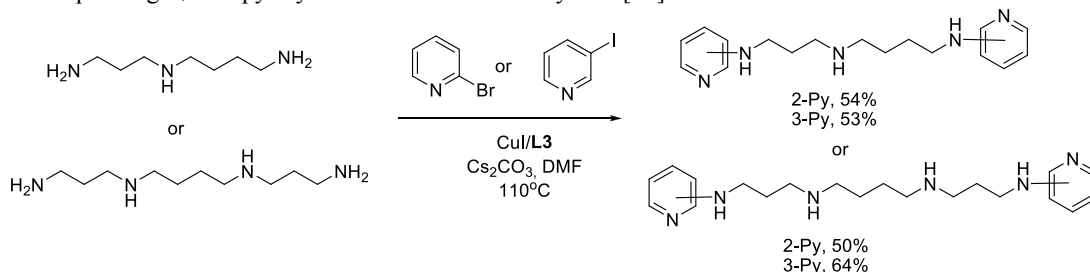
Naturally occurring polyamines can be equally transformed into their *N,N'*-diaryl derivatives and the application of the appropriate catalytic systems may improve the balance between the arylation of the primary and secondary amino groups (Scheme 13). The dependence of the target compounds yields on the nature of the substituent was also essential, the most problematic were the reactions with *p*-iodoanisole, which smoothly proceeded only in the presence of 20 mol% of the catalyst [61].

corresponding products in yields up to 68–76%. In general, the increase in the number of ethylenediamine units in the molecules of polyamines led to an easier heteroarylation of the secondary amino groups while trimethylenediamine units disfavored diarylation and promoted the formation of the monopyridyl derivatives.



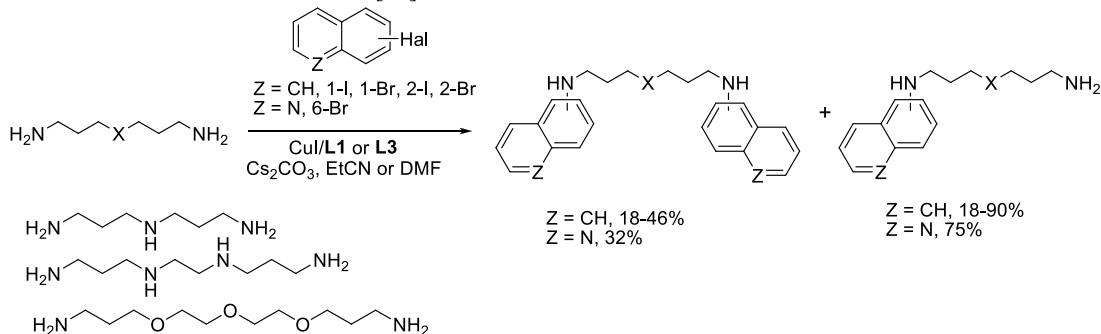
Scheme 16: Cu(I)-catalyzed *N,N'*-diheteroarylation of the tetraamines.

Better results were obtained with the natural spermidine and spermine (Scheme 17). The use of 2-bromo- or 3-iodopyridine in the presence of CuI/L3/DMF catalytic system and running the reaction at 110°C allowed the synthesis of the corresponding *N,N'*-dipyridyl derivatives in 50–64% yields [64].



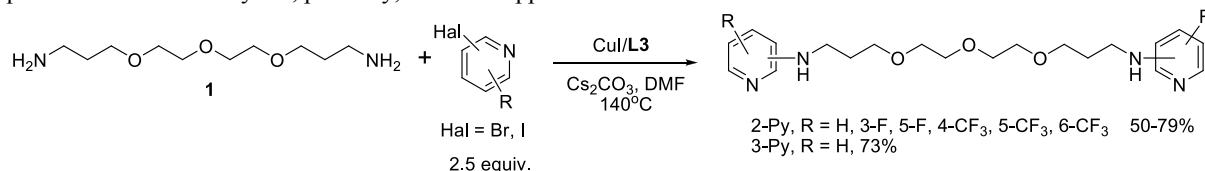
Scheme 17: Cu(I)-catalyzed *N,N'*-diheteroarylation of the naturally occurring tri- and tetraamines.

The introduction of the fluorophore groups like naphthalene and quinoline in polyamines is also possible via Cu(I)-catalyzed amination (Scheme 18). Note that 1-iodo or 1-bromonaphthalenes possess lower reactivity in these reactions and gave mainly monoarylated derivatives, whereas 2-iodonaphthalene and 6-bromoquinoline were more reactive, especially in the reactions with the tetraamine [66].



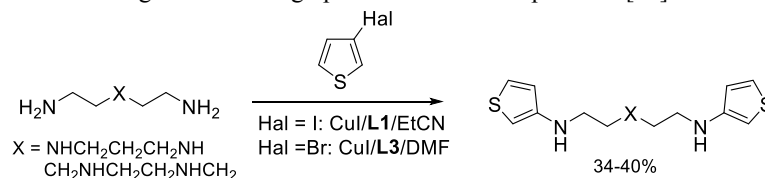
Scheme 18: Cu(I)-catalyzed *N,N'*-di(hetero)arylation using 1- and 2-halogenonaphthalenes and 6-bromoquinoline.

The heteroarylation of the trioxadiazamine with 2- and 3-iodopyridine proceeds easily in the presence of CuI/L3 system in DMF giving 57 and 73% yields, respectively, of the *N,N'*-dipyridyl derivatives (Scheme 18). It was shown possible to carry out the diheteroarylation of the same diamine with a series of substituted 2-bromopyridines bearing F and CF₃ substituents. The yields were good in all cases, and the reaction with a sterically hindered 3-fluoro-2-bromopyridine provided the best 79% yield, probably, due to a suppression of the side reactions.



Scheme 19: Cu(I)-catalyzed *N,N'*-diheteroarylation of trioxadiazine with the 2- and 3-iodopyridine and fluorine-containing 2-bromopyridines.

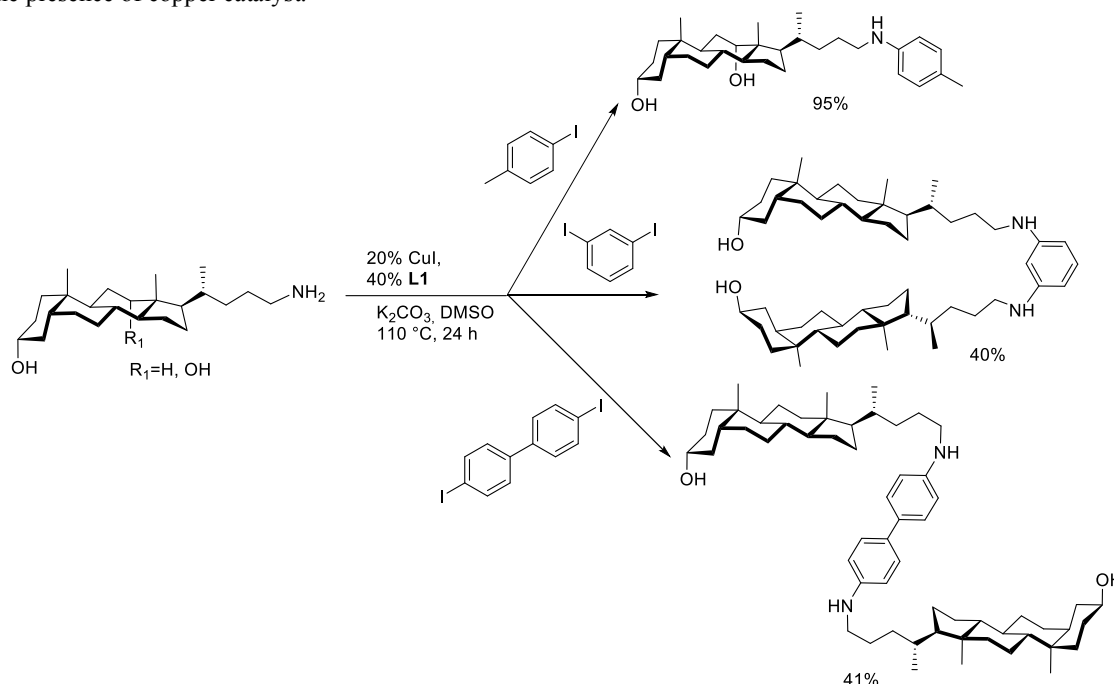
We also demonstrated the possibility to introduce 3-bromo- and 3-iodothiophenes in the reactions with polyamines, the catalytic systems with **L1** and **L3** ligands were enough efficient (Scheme 20). However the yields were moderate, first of all, due to difficulties during the chromatographic isolation of the products [67].



Scheme 20: Cu(I)-catalyzed *N,N'*-diheteroarylation of the tetraamines with 3-halogenothiophenes.

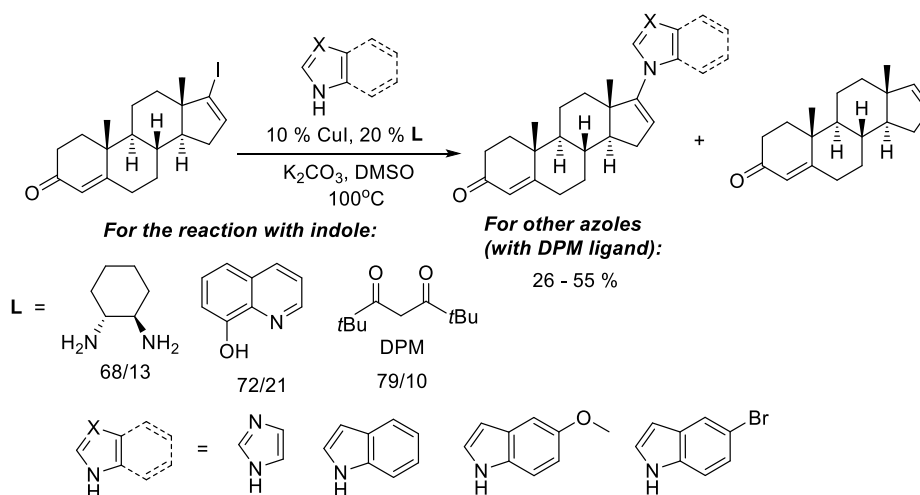
6 Cu(I)-catalyzed C-N bond formation in the transformations of steroids

24-Amino derivatives of the cholanol were shown to participate in the Cu(I)-catalyzed amination: the reaction with *p*-iodotoluene catalyzed with Cu/L1 using K_2CO_3 as a base and run in DMSO at 110°C provided almost quantitative yield of the desired product (Scheme 21), and the reactions with 1,3-diiodobenzene or 4,4'-diiodobiphenyl afforded bissteroid derivatives in quite reasonable yields [68]. This reaction is a rare example of the diamination of dihaloarenes in the presence of copper catalyst.



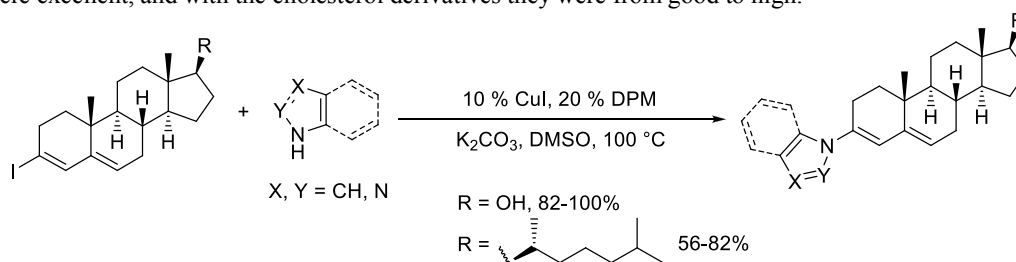
Scheme 21: Cu(I)-catalyzed amination reaction in the functionalization of steroids and synthesis of steroid dyads.

The amination of 17-iodoandrosta-4,16-dien-3-one with indole demanded a search for the ligand able to suppress the catalytic reduction of the iodine (Scheme 22). 2,2,6,6-Tetramethylheptane-3,5-dione (DPM) was found to serve better than 8-hydroxyquinoline or cyclohexane-1,2-diamine, and using this catalytic system the amination with 5-substituted indoles and imidazole was carried out [69].



Scheme 22: Cu(I)-catalyzed vinylation of indoles and imidazole using 17-iodoandrosta-4,16-dien-3-one.

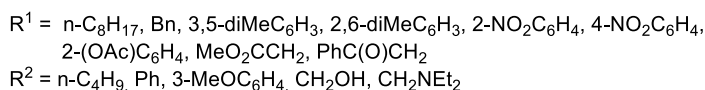
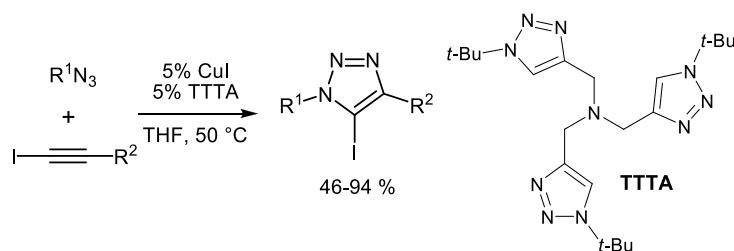
The same approach was successfully applied to the amination of another iodostereoid possessing the halogen atom at position 3 (Scheme 23). The scope of azoles was substantially enlarged, they included not only substituted indoles and imidazoles, but also pyrazoles and carbazoles. In the case of 3-iodo-17-hydroxyandrostadiene the yields were excellent, and with the cholesterol derivatives they were from good to high.



Scheme 23: Cu(I)-catalyzed amination of 3-iodosteroids with various azoles.

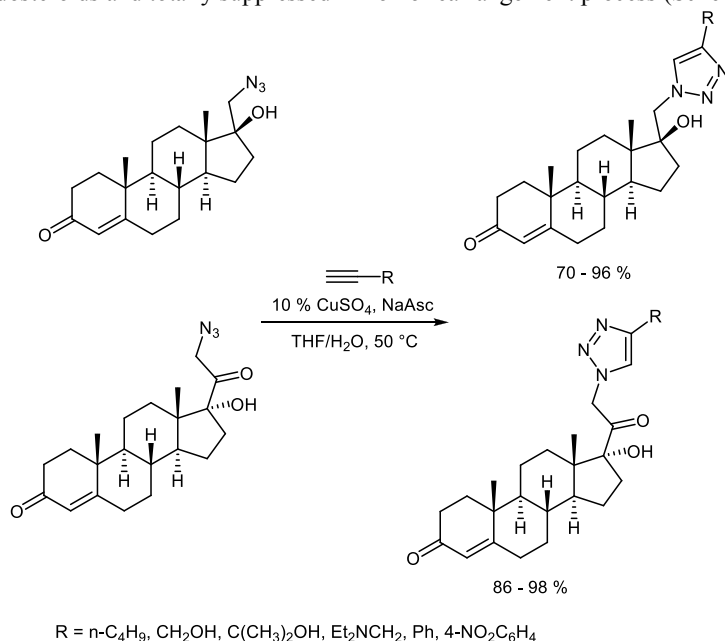
7 Huisgen 1,3-dipolar cycloaddition in the formation of diverse conjugates

Copper-catalysed alkyne-azide cycloaddition (CuAAC, “click”) is a novel synthetic tool with a remarkable practical and ecological impact and widely employed in the synthesis of many functional molecules including pharmaceuticals, dyes, sensors, and bioconjugates [70-77]. This reaction allows to deliver sophisticated molecules or libraries of substituted 1,2,3-triazoles due to its selectivity, excellent functional compatibility, reliability and simplicity of experimental conditions. This reaction was employed by us for several purposes. The first is the synthesis of 5-iodo-1,2,3-triazoles in view of their further catalytic modifications employing a reactive C-I bond. The reactions of a variety of organic azides with several terminal acetylenes were conducted using CuI and TTTA ligand providing the desired products in yields from moderate to excellent and the modified protocol tolerated the presence of various functional groups [78]. (Scheme 24).

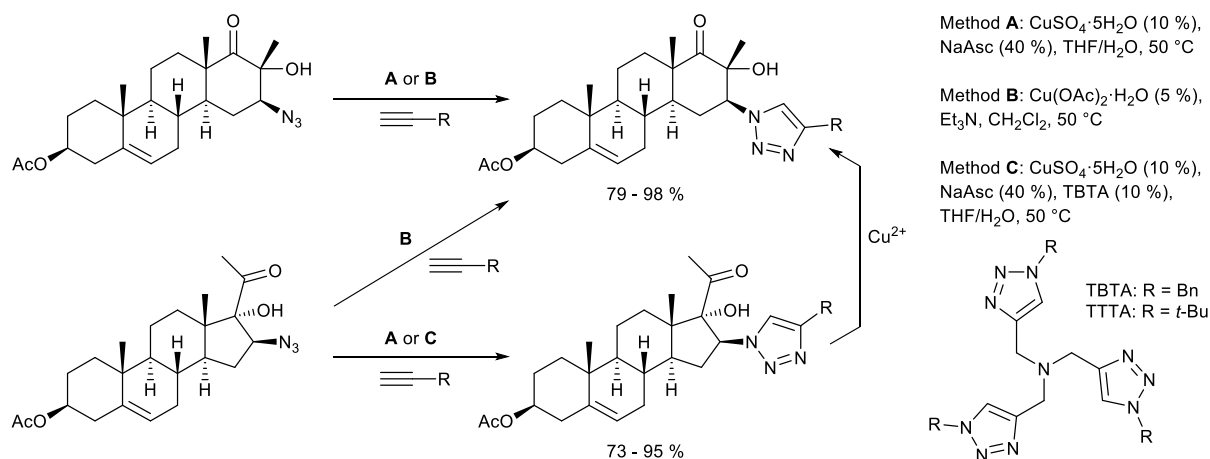


Scheme 24: Synthesis of 5-iodo-1,2,3-triazoles.

Then functionalisation of steroids bearing primary azido substituent in the side chains located at position 17 of the steroid scaffold was investigated (Scheme 25). The resulting triazolyl-substituted steroids were obtained in high to excellent yields using various terminal alkynes including those with hydroxyl groups [79]. Steroids with azido substituent at position 16 were also studied in CuAAC reaction (Scheme 26). The reactions of these more sterically hindered compounds proceeded more slowly and demanded the modification of the reaction conditions. The use of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ and NaAsc in aqueous THF (method A) allowed the reaction of azidosteroids with propargyl alcohol, while the catalytic system with Et_3N (method B) appeared effective for both phenylacetylene and 1-hexyne. Finally, the catalytic system comprising $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$, tris(benzyltriazolylmethyl)amine (TBTA) and NaAsc (method C) allowed to achieve complete conversion of azidosteroids and totally suppressed D-homo rearrangement process (Scheme 26).

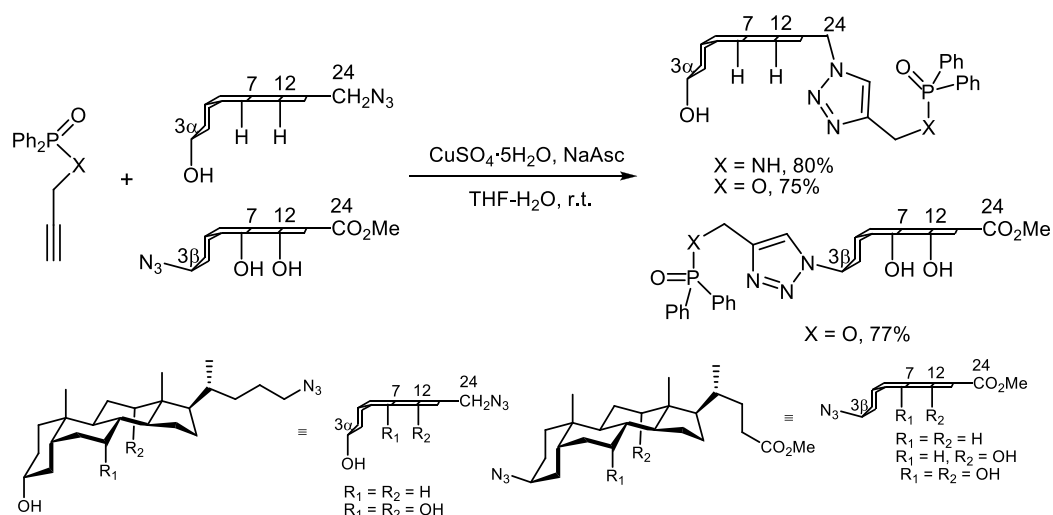


Scheme 25: Synthesis of triazolyl derivatives from steroids bearing primary azido groups.

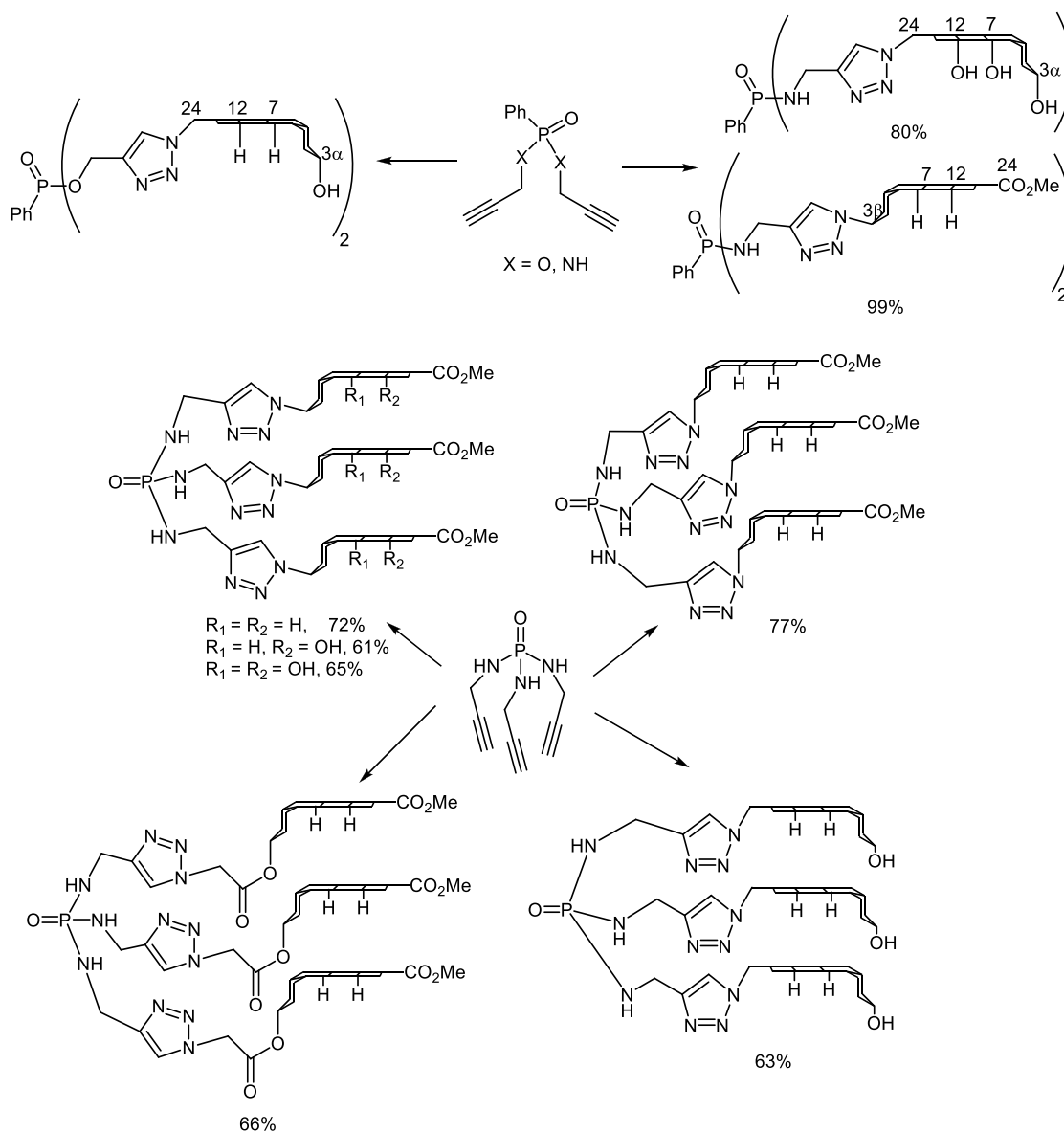


Scheme 26: Synthesis of triazolyl derivatives from steroids bearing secondary azido groups.

CuAAC reaction was successfully employed for the preparation of a series of steroid dipods and tripods based on the central phosphorus acids, comprising anion binding triazolium sites and hydrophobic cholane residues [80, 81]. Propargyl phosphorus esters first reacted with the steroid derivatives bearing azido group at various positions to obtain 1:1 conjugates and to optimize the reaction conditions (Scheme 27).



Scheme 27: Click reaction in the steroids modifications.



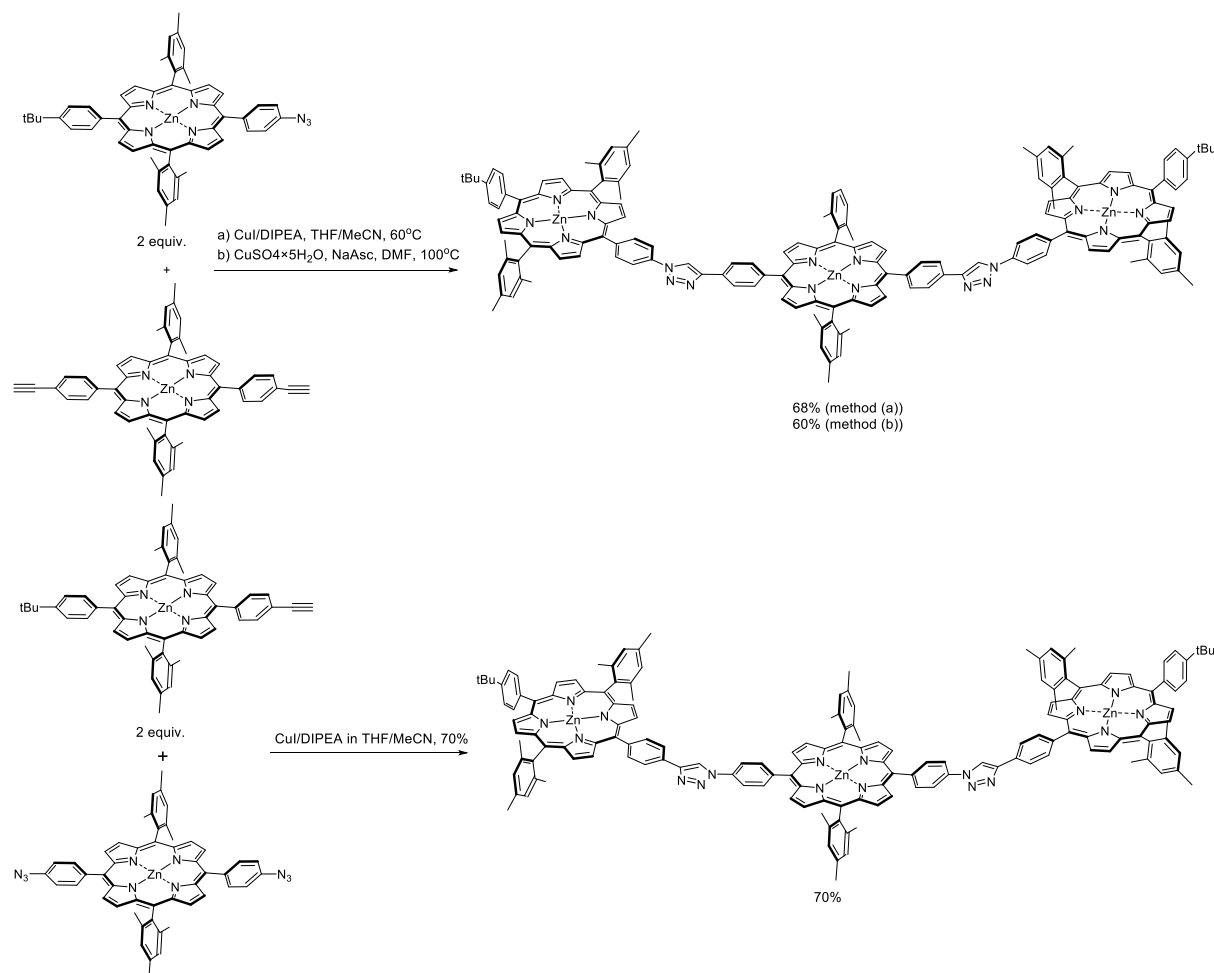
Scheme 28: Synthesis of dipodal and tripodal ligands – derivatives of cholanes – using click strategy.

Dipropargyl derivative appeared to be significantly less reactive than the monopropargyl-containing diphenylphosphinate, however, excellent yields were obtained when the temperature was raised to 60°C. The same conditions

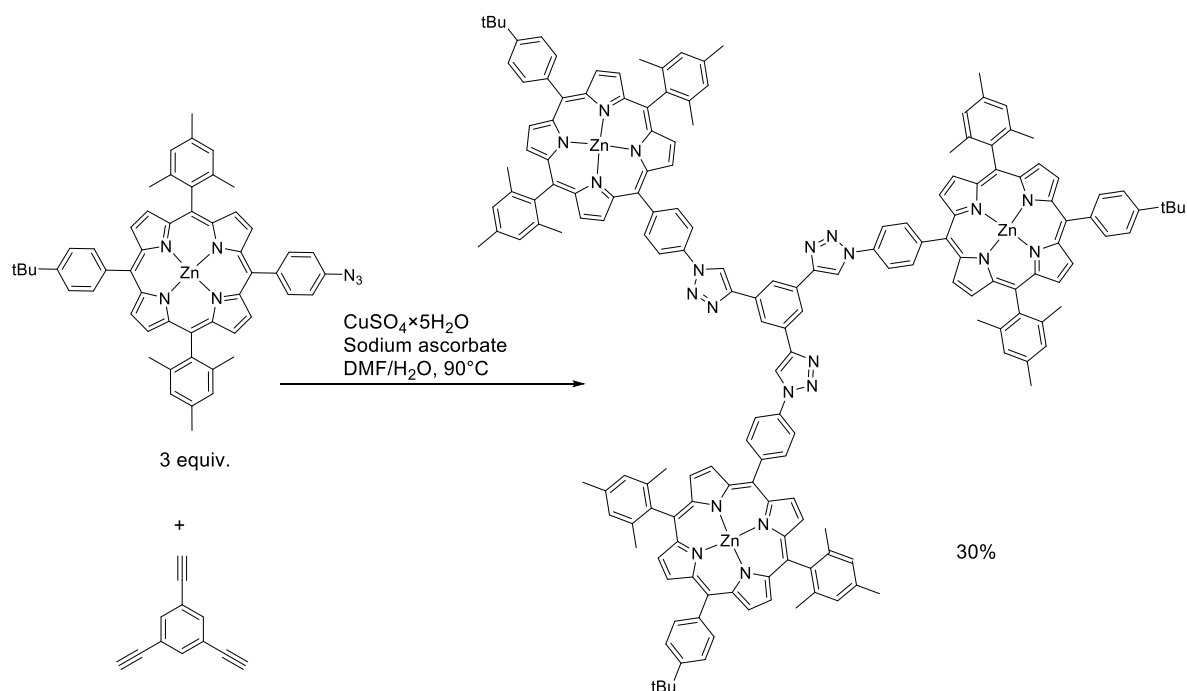
were applied for the preparation of the bile acid based tripods (Scheme 28). Good yields were obtained for 3 β -, 3 α -, and 24-cholanetriazolyl derivatives. Slightly higher yields were observed for lithocholic acid-based tripod in comparison with deoxycholic and cholic acid based products. Also we obtained a click adduct with 3-azidoacetoxycholine derivative. These di- and tripodal compounds in which steroidal units are organized around the phosphorus center via triazolyl linkers are of interest for anions binding studies.

Cu(I)-catalyzed 1,3-dipolar cycloaddition reactions were successfully used for the synthesis of porphyrin triads containing 1,2,3-triazole linkers. For this purpose two combinations of starting compounds were tried. The first reaction scheme employed 5,15-bis(ethynylphenyl) derivative of porphyrin with 2 equiv. of *meso*-(4-azidophenyl)substituted porphyrin (Scheme 29). The reaction conditions were adjusted to provide the high yield of the target trisporphyrin compound, the best were found to be CuI/DIPEA in THF-MeCN solution which gave 68% yield of this triad, a classical system (CuSO₄/sodium ascorbate in DMF) provided slightly lower yield 60%. [82]. According to the second reaction route, 5,15-bis(4-azidophenyl)-substituted porphyrin was coupled with 2 equiv. of *meso*-(4-ethynylphenyl)porphyrin in the presence of CuI/DIPEA in THF-MeCN (Scheme 29) and it produced an isomeric porphyrin triad in a high 70% yield. It was also shown that a simpler porphyrin dyad could also be easily synthesized by reacting corresponding porphyrins under the same conditions.

Porphyrin triad of a star shape was successfully synthesized using the similar approach: 1,3,5-tri(ethynyl)benzene was reacted with 3 equiv. of *meso*-(4-azidophenyl)-substituted porphyrin and the target star-shaped triad was isolated in 30% yield (Scheme 30) [83]. It is to be mentioned that only zinc porphyrinates but not free porphyrin bases can participate in these reactions as the latter easily coordinate copper(II) hampering the catalytic reaction.



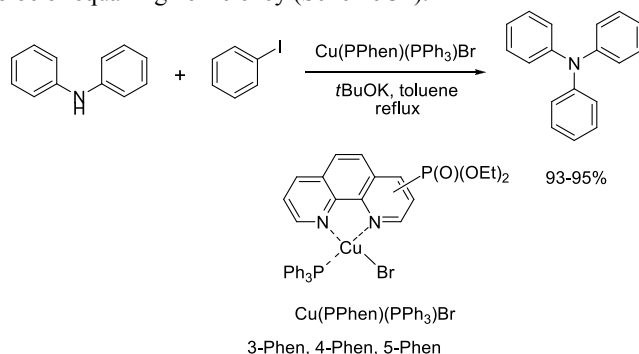
Scheme 29: Triazolyl linkers in the synthesis of the porphyrin triads.



Scheme 30: Synthesis of the star-shaped porphyrin triad using click strategy.

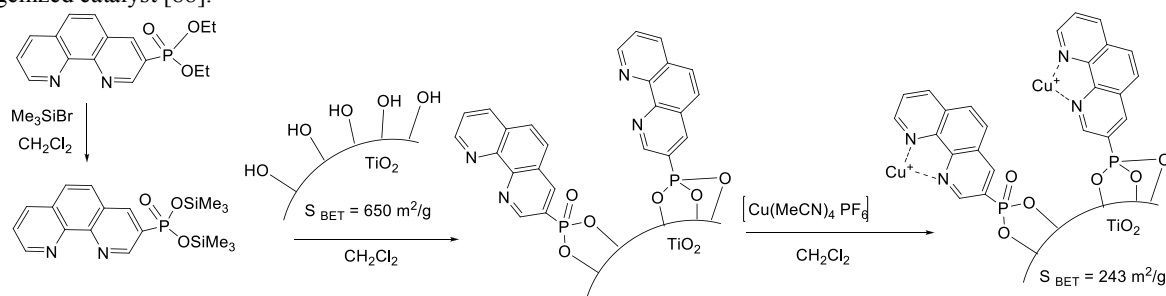
8 Heterogenized copper catalysis in C-N bond formation

In the last two decades, significant improvements in homogeneous Cu-catalyzed C–C and C–Het (Het: O, S, Se, N, P) cross-coupling reactions, additions to unsaturated C–C bonds, Huisgen 1,3-dipolar cycloaddition, and other organic transformations were reported. Homogeneous catalysts are well suited for increasing the reaction scope and the tuning the reaction rate and its selectivity. However, the separation of organic products from toxic copper compounds are particularly troublesome due to the exceptional coordination properties of this metal, which avidly bind a huge range of organic molecules containing oxygen and nitrogen donor sites. To overcome this drawback and open the route to industrial use of these catalytic reactions, the heterogenization of homogeneous copper catalysts are widely studied. A promising approach to robust catalytic materials is a direct immobilization of relevant copper complexes onto solid supports. For this purpose we developed a synthetic approach to phosphonate-substituted 1,10-phenanthroline derivatives [4], investigated their coordination [85, 86] and catalytic properties of related copper(I) complexes [87]. These complexes are efficient catalyst for a wide range of catalytic reactions including C–N coupling and can be immobilized on titania oxide supports [88]. In order to investigate the possibilities of the heterogenized copper catalysts to promote various coupling reactions, at first the synthesis of Cu(I) complexes with 1,10-phenanthrolines with the phosphoryl groups at positions 2, 3, 4, and 5 was undertaken [87]. The efficiency of these complexes was studied in the model reaction of the diphenylamine arylation with the simplest iodobenzene. The complexes with 3-, 4- and 5-diethylphosphoryl substituted phenanthrolines were found to be of equal high efficiency (Scheme 31).



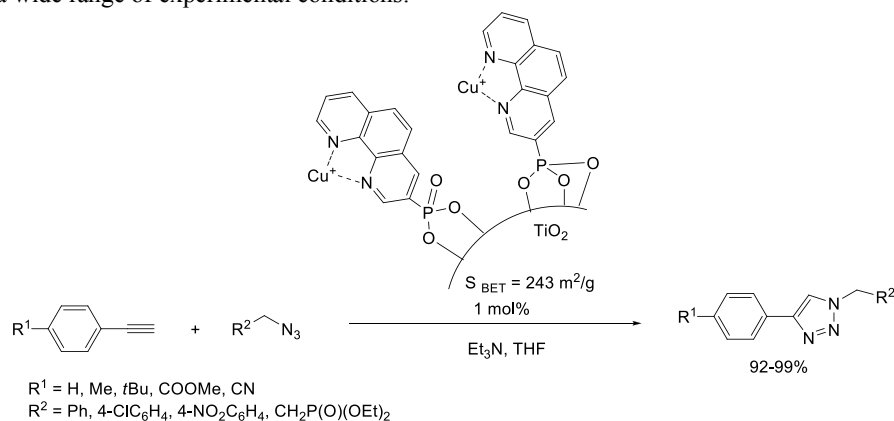
Scheme 31: Copper catalysts comprising phosphonate-substituted 1,10-phenanthroline ligand.

Following these results, the free 3-diethoxyphosphoryl-1,10-phenanthroline ligand was grafted on the surface of hydrated mesoporous titania followed by the complexation of copper ions, as shown in Scheme 32, to produce a heterogenized catalyst [88].



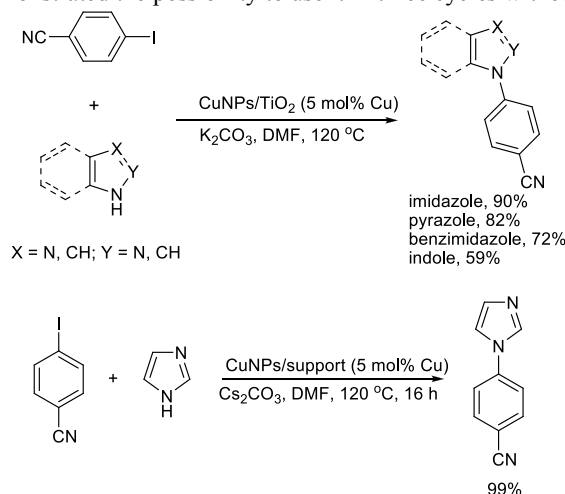
Scheme 32: Grafting of copper catalysts on the surface of hydrated mesoporous TiO_2 .

An excellent catalytic performance of the catalyst and its reusability in Huisgen 1,3-dipolar cycloaddition was demonstrated (Scheme 33). Moreover, this catalyst was found to be suitable for Sonogashira coupling and addition. Fairly low catalyst loading, simple recovery and reuse (up to ten times) of the solid were achieved in all studied reactions proceeding through principally different reaction pathways. This catalytic versatility of the copper catalyst is highly desirable for sustainable chemistry but still rarely reported owing to the challenge in the preparation of robust catalysts applicable for a wide range of experimental conditions.



Scheme 33: Catalytic properties of the grafted copper(I) complex with 1,10-phenanthroline ligand.

We investigated the immobilization of copper nanoparticles (CuNPs) on various supports and used these solid catalysts in the C-N bond formation [89]. The model reaction included the amination of *p*-iodobenzonitrile with various azoles like imidazole, pyrazole, benzimidazole and indole (Scheme 34). TiO_2 support was found to be the best among other tested (carbon, zeolite, montmorillonite-K10 clay) and the yields ranged from 59 to 90%. Using the model reaction with imidazole Cs_2CO_3 was found to be superior to K_2CO_3 as it provided almost quantitative yields on different supports. Using CuNPs/C catalyst we demonstrated the possibility to use it in three cycles without loss of efficiency.



Scheme 34: CuNPs on various supports in the arylation of azoles.

9 Conclusions

As a result of our investigations in the field of the application of copper (I) catalysis in the formation of C-N bonds we may conclude that it can be seen as an efficient alternative to expensive Pd(0)-catalyzed amination in such fields as the amination of (hetero)aryl halides with adamantane-containing amines and various di- and polyamines. In the latter case we focused our attention at the *N,N'*-di(hetero)arylation and found out that this process is quite possible with the diamines, oxadiazines and polyamines. Comparing the efficiency of the Cu(I)-catalyzed amination with Pd-mediated processes, the advantage of the first is almost full absence of the side reactions of *N,N'*-di(hetero)arylation of the primary amino groups in the majority of cases, on the other hand, steric hindrances become more important and may hamper the reactions. Also, in the case of diamines and oxadiazines the formation of monoarylated products may be more pronounced as well as the side reactions of the arylation of the secondary dialkylamino groups in polyamines. The right choice of the catalytic system helping to suppress side reactions and promoting the formation of the desired *N,N'*-diaryl derivatives is always important. The amination reactions catalyzed by Cu(I) complexes were extended to modifications of steroids with various N-containing heterocycles. Click reactions were successfully employed for the preparation of bis- and tris(steroid) systems (dipods and tripods) for further application in the anion binding studies. These reactions were also important in the synthesis of porphyrin triads of various architectures. Several heterogenized copper catalysts were also investigated to propose reusable catalytic systems.

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