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Review

Recent Achievements in the Copper-Catalyzed Arylation of Adamantane-Containing Amines, Di- and Polyamines

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Abstract: Rapid development of the copper-catalyzed amination of aryl halides in the beginning of the 21st century, known as the Renaissance of the Ullmann chemistry, laid foundations for the use of this method as a powerful tool for the construction of the C(sp^2)-N bond and became a rival of the Buchwald–Hartwig amination reaction. Various applications of this approach are well-documented in a number of comprehensive and more specialized reviews, and this overview in the form of a personal account of the Cu-catalyzed arylation and heteroarylation of the adamantane-containing amines, and di- and polyamines, covers a more specific area, showing the possibilities of the method and outlining general regularities, considering reagents structure, copper source and ligands, scope, and limitations. The material of the last decade is mainly considered, and recent data on the application of the unsupported copper nanoparticles and possibilities of the Chan-Lam reaction as an alternative to the use of aryl halides are also discussed.

Keywords: copper; catalysis; amination; amines; polyamines; aryl halides; adamantane; nanoparticles

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1. Introduction

The beginning of the 20th century was marked by the birth of the copper-mediated reactions of carbon–carbon and carbon–heteroatom bond formation. In the pioneer research carried out by Ullmann and Goldberg, copper powder was shown to provide access to biphenyls [1], aryl amines [2], diaryl ethers [3], and *N*-aryl amides [4]. These reactions employed stoichiometric amounts of copper and strong bases, and demanded very harsh conditions; thus, the substrates' scope was strictly limited. However, the simplicity of the approach allowed for the synthesis of a series of valuable compounds via C–C, C–M, C–O, and C–S bond formation, and some "classical" reactions of this type are still used in industry [5–8].

The need for compounds bearing the *N*-(hetero)aryl moiety cannot be overestimated. They are widely used in the synthesis of pharmaceuticals [9,10] and agrochemicals [11,12], and for the fabrication of modern organic materials [13,14]. It is obvious that convenient, reliable, and inexpensive methods for the synthesis of compounds with the C(sp^2)–N bond are always highly demanded. The so-called "Renaissance of the Ullmann chemistry" dates back to the beginning of the 21st century and is associated with the application of the ligands which allowed for the use of copper in catalytic amounts and the application of rather mild reaction conditions. To note, the effect of ketones or esters on the rate of the Ullmann reactions was noted even in 1964 [15]; however, at that time, it was thought to be a result of a better solubility of the copper compounds. In 1997, the reaction of phenols with aryl halides containing triazene fragments at the *ortho* position was reported [16], and this fragment was described as an appended ligand for the copper catalyst. A real breakthrough was a series of works by Buchwald [17], Ma [18], and Taillefer [19] which

used the catalytic systems on the basis of in situ-formed Cu(II) complexes with various ligands. This approach proved to be exceedingly fruitful and further development of the Cu-catalyzed amination and amidation reactions has been decisively linked with the design and investigation of the ligands [20,21]. These ligands can be divided into three main groups: N,N-ligands [22–26], N,O-ligands [27–31], and O,O-ligands [32–36], of which the most widely used and efficient representatives are shown in Figure 1. The role of the anionic ligands, which favor the oxidative addition and thus ensure milder conditions and a wider scope of the aryl halides, was emphasized in [37–39], the oxalamide ligands being essentially efficient for this purpose [40–42].

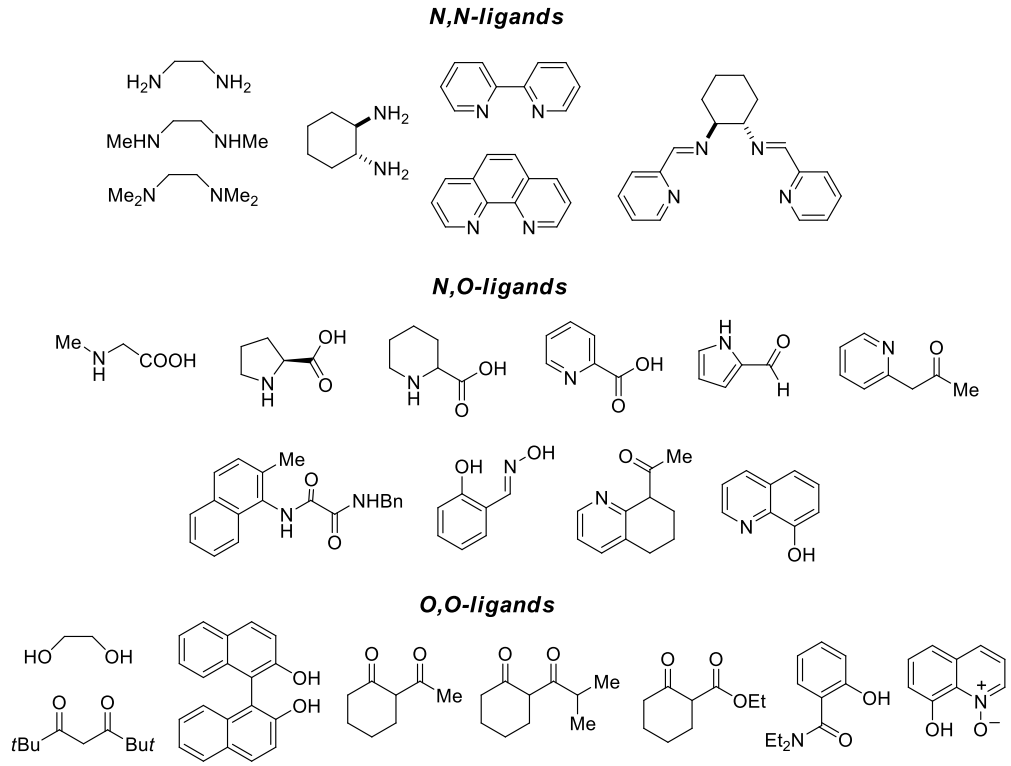


Figure 1. Most important ligands for Cu-catalyzed C–N bond formation.

The development of the copper-catalyzed amination has been already described in several comprehensive reviews. Two of them were published before 2010 by Ma [43] and Taillefer [19]. Two other reviews are dedicated to the comparison of the copper- and palladium-catalyzed amination reactions [44,45]. Further, a more thorough review has been published [46], and some accounts emphasize the application of the method to the synthesis of natural compounds [47,48]. During the last decade, the achievements in the copper-catalyzed amination became a focus of three comprehensive studies [49–51], and special cases of this approach have also been discussed recently [52,53].

One of the important trends in the study of the Cu-catalyzed amination and amidation reactions is the use of heterogeneous and heterogenized copper catalysts immobilized on various supports. The most frequently used copper salt for this purpose is CuI. The nature of supports is versatile, and different organic linkers may serve as the ligands for the copper cation. Cu catalysts are often immobilized on polymer supports [54–60]. For the needs of the development of reusable catalysts, those containing magnetite particles were found to be especially attractive [61–64].

The studies on the mechanism of Cu-catalyzed amination put forward several hypotheses. Taking into consideration the fact that copper in different oxidation states can be successfully employed in catalysis, it was supposed that Cu(I) is a genuine catalytic particle which emerges in the course of the reduction process of Cu(II) compounds [15,65–67]. In some protocols, additional reagents such as ascorbic acid are added to ensure this

reduction [68,69], but many others do not envisage any special reductant [70,71]. In the case of Cu(0), it is thought that, on contrary, its oxidation into Cu_2O gives rise to a catalytically active Cu(I) [65,72]. The main types of proposed mechanisms are the following: (1) oxidative addition of ArHal leading to Cu(III) complex followed by the reductive elimination; (2) formation of the π-complex of aryl halide with Cu(I) followed by the nucleophilic substitution; (3) single electron transfer (SET) or hydrogen atom transfer (HAT); (4) σ-bond metathesis. The majority of researchers support the idea of a key role of Cu(III) intermediate [46,73–77]; for this purpose, some researchers synthesized several stable complexes of Cu(III) in order to study the coordination sphere of the metal cation and to carry out their reactions with nucleophiles [78–80]. Ma investigated a series of reactions without additional ligands and postulated that, in this case, aryl halides, acting as ligands, form the π-complexes with the copper cation [27]. SET and HAT mechanisms involving radicals were thought to be verified [66] by the use of the radical traps which hindered the reactions. At last, metathesis with a four-membered transition state was proposed by Bacon [81]; this mechanism suggests the coordination of the copper cation with the halogen atom of ArHal. It is quite plausible that, with different reagents and in the presence of various ligands, different mechanisms can be actualized.

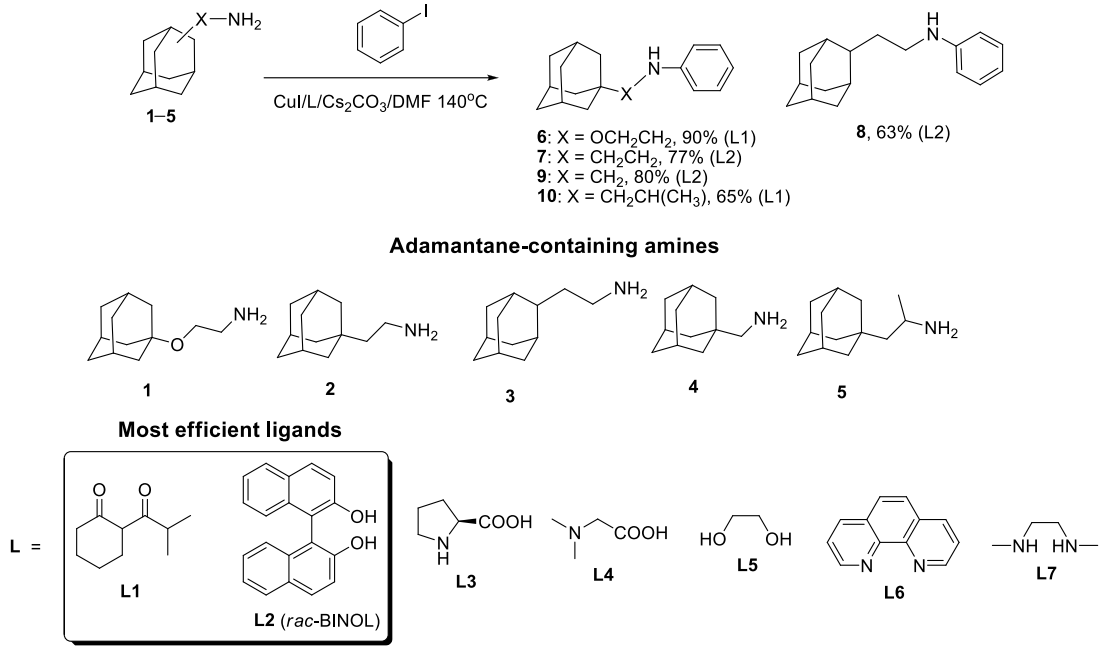
Our research interests in the field of Cu-catalyzed amination cover the reactions with adamantane-containing amines, diamines, oxadiamines, and polyamines. These substrates are interesting due to their often complicated and unpredictable reactivity in spite of the fact that the reactions proceed at primary amino groups. The outcome of the reactions is strongly dependent on the spatial environment of the amino group in the case of adamantaneamines, and the number of methylene groups, or oxygen or nitrogen atoms in the chain for di- and polyamines. Previously, we thoroughly studied the (hetero)arylation of these compounds in the presence of palladium catalysts [21] and found the scope and limitations of this approach. In the following investigations, we compared the possibilities of the application of a much cheaper copper and found the regularities of this process. Our ongoing research deals with the employment of the copper nanoparticles instead of the homogeneous CuI-catalyzed reactions as well as the search for new applications of the Chan-Lam reaction; the present review will describe all of these versions of the C(sp^2)-N bond formation. The main objective of this review is to show the scope and limitations of the copper catalysis with regard to the arylation and heteroarylation of these amines, and the following aspects will be addressed: the dependence of the most appropriate catalytic system on the nature of reagents, possibilities of *N*,*N*′-di(hetero)arylation of the diamines, oxadiamines, and polyamines, the use of unsupported copper nanoparticles, and the character of the Chan–Lam amination employing adamantaneamines, diamines and oxadiamines.

2. CuI-Catalyzed Arylation of Adamantane-Containing Amines

Adamantane-containing amines and their derivatives are well-known for their versatile biological activity; it is sufficient to mention that amantadine (adamantane-1-amine hydrochloride) has been used as an antiviral and antiparkonsonian drug for decades [82], memantine for the treatment of Alzheimer's disease [83], and bromantane (N-(4-bromophenyl)adamantane-2-amine) [84] and its fluorine-containing analogue [85] as neurostimulation agents. Thus, it is quite natural that, previously, we paid much attention to the elaboration of efficient methods of *N*-(hetero)arylation of the adamantane-containing amines employing Pd(0)-catalyzed amination reactions.

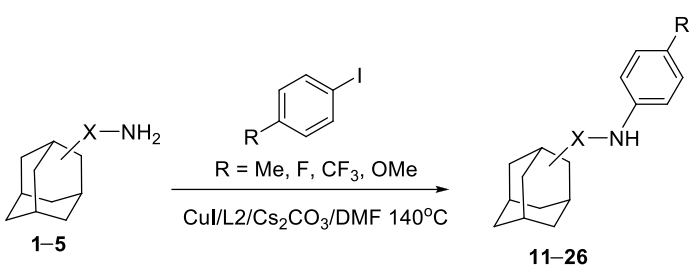
In the trend of replacing expensive palladium catalysis with much cheaper copper-catalyzed reactions, we carried out an investigation of the arylation of a series of adamantane-containing amines, **1**–**5**, differing by the steric hindrances at the amino group, with a model iodobenzene in the presence of various copper catalysts (Scheme 1) [86]. Several widely employed ligands, L1–L7, were tested in the reaction and two of them, L1 (2-isobityrylcyclohexanone) and L2 (*rac*-BINOL (BINOL = 2,2′-bi(1-naphthol)), both O,O-type, were found to be the most efficient in the reactions run in DMF at 140 °C and catalyzed

by a standard CuI in the presence of Cs_2CO_3. Other solvents which were tested such as propionitrile (EtCN) gave poorer yields, as well as did other copper sources (CuBr, CuOAc, CuOTf, Cu_2O, and CuO). Depending on the structure of the amine, they provided the yields of the *N*-arylation products in the range of 63–90% and were further used for the reactions with adamantane-containing amines. The highest yield (compound **6**, 90%) was observed in the reaction with the amine **1**, in which the amino group is located furthest from the adamantane core. The attempt to use bromobenzene instead of iodobenzene resulted in a dramatic diminishing of the product yield.



Scheme 1. CuI-catalyzed *N*-arylation of the adamantane-containing amines with iodobenzene.

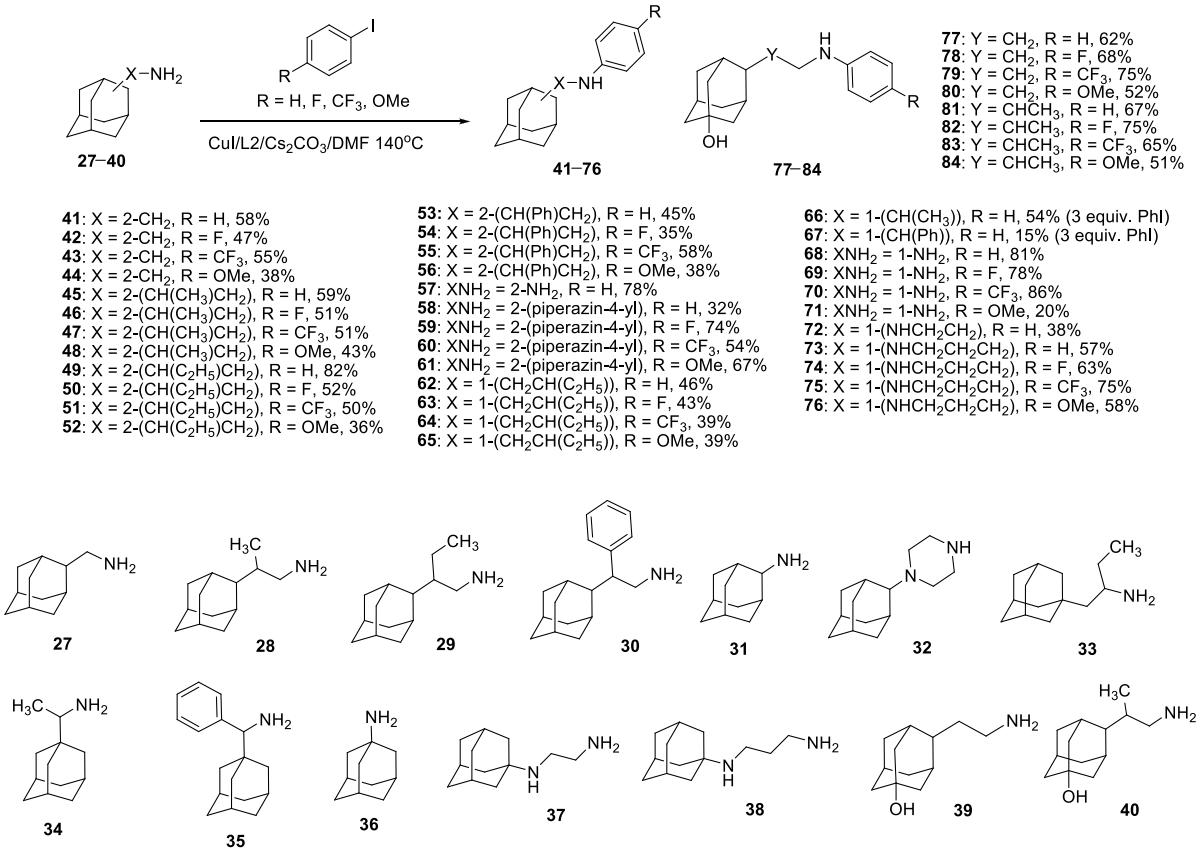
The same amines, **1**–**5**, were introduced in the reactions with *para*-substituted iodobenzenes containing typical electron donor and electron withdrawing substituents (Scheme 2). It was interesting to follow the dependence of the yields of the *N*-arylated products; however, in the majority of cases, they ranged from 50 to 75%, and the advantage of the electron deficient 4-iodotrifluoromethylbenzene over electron donor 4-iodoanisole was quite moderate. Thus, in the reactions of **1**–**4**, CF_3-containing products **12**, **15**, **19**, and **22** were obtained in 55–79% yields, while MeO-containing products **13**, **16**, **20**, and **23** were synthesized in 44–65% yields. Only more sterically hindered amine **5** gave generally lower yields with all of the iodobenzenes which were tested (compounds **24**–**26**).



11: X = 1-(OCH_2CH_2), R = F, 50%
12: X = 1-(OCH_2CH_2), R = CF_3, 55%
13: X = 1-(OCH_2CH_2), R = OMe, 45%
14: X = 1-(CH_2CH_2), R = F, 74%
15: X = 1-(CH_2CH_2), R = CF_3, 79%
16: X = 1-(CH_2CH_2), R = OMe, 44%
17: X = 2-(CH_2CH_2), R = Me, 75% (L1)
18: X = 2-(CH_2CH_2), R = F, 70%
19: X = 2-(CH_2CH_2), R = CF_3, 75%
20: X = 2-(CH_2CH_2), R = OMe, 65% (L1)
21: X = 1-CH_2, R = F, 61%
22: X = 1-CH_2, R = CF_3, 61%
23: X = 1-CH_2, R = OMe, 52%
24: X = 1-($CH_2CH(CH_3)$), R = F, 49%
25: X = 1-($CH_2CH(CH_3)$), R = CF_3, 48%
26: X = 1-($CH_2CH(CH_3)$), R = OMe, 29%

Scheme 2. CuI-catalyzed *N*-arylation of the adamantane-containing amines with *para*-substituted iodobenzenes.

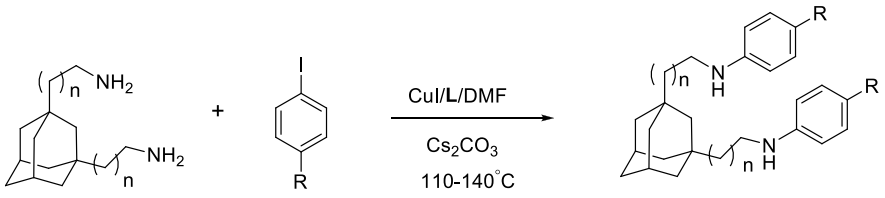
The extension of the series of the adamantane-containing amines (compounds **27**–**40**) was undertaken to reveal the dependence of the amines' structure on the outcome of the copper-catalyzed *N*-arylation (Scheme 3) [87]. The reactions were run under optimized conditions with iodobenzene and its several *p*-substituted analogues. The amines **27**–**29**, **31**, **32**, **36**, and **38**–**40** provided similar results as described above, obviously, due to a lack of notable steric hindrances. The yields of the corresponding derivatives with the methoxy group were somewhat lower and ranged from 36 to 58%. To note, the presence of the hydroxyl group in the amines **39** and **40** did not alter its good reactivity in the N-arylation reactions. In the case of the amines **30** and **33**, steric hindrances were more pronounced, which led to diminished yields of the corresponding products **53**–**56** and **62**–**65**. Amines **34** and **35** were less reactive and the use of three equiv. of iodobenzene was inevitable, allowing for a 54% yield of the product **66,** but only a 15% yield of **67**. The reactivity of the amine **37** was also substantially lower than that of its analogue, **38**, probably due to the presence of the ethylenediamine moiety in the first, which could better bind copper than the $NCH_2CH_2CH_2N$ fragment in **38**, thus removing it from the catalytic cycle.



Scheme 3. CuI-catalyzed *N*-arylation of a variety of adamantane-containing amines with iodobenzenes.

The possibility to conduct an *N*,*N*′-diarylation reaction of the adamantane-containing diamines **85** and **86** was shown using several iodobenzenes (Scheme 4) [88]. Depending on the substituent in iodobenzene, ligand L1 or L2 was found to be optimal. Better yields were obtained with the diamine **85**, where amino groups are located further form the adamantane core, and the yields of the corresponding derivatives **87**–**92** ranged from 50 to 79%. It is interesting that the best yield was observed in the reaction with the electron-enriched *p*-iodoanisole (compound **92**), probably due to fewer side reactions with this less active iodide. In the reactions with the diamine **86**, generally, the yields of the diarylated products were notably lower, and several by-products were isolated, evidencing a substantial contribution of the formation of the amine-imine followed by its transformation into the corresponding aldehyde and subsequent processes.

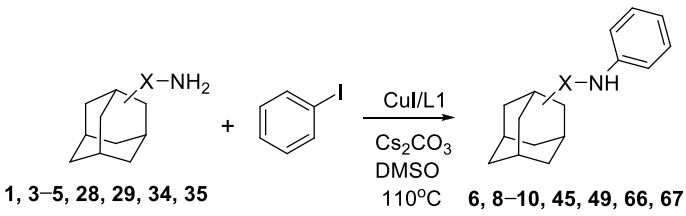
A special investigation was dedicated to the possibilities of the reactions run in DMSO instead of DMF [89]. The reactions with various amines, **1**, **3**–**5**, **28**, **29**, **34**, **35**, featuring a different spatial environment of the amino group were carried out with iodobenzene at 110 °C (Scheme 5). The results were quite comparable with those obtained in DMF at 140 °C; moreover, the arylation of the most hindered amines, **34** and **35**, allowed for increasing the yields of the corresponding derivatives, **66** and **67**, when three equiv. of PhI were employed. The reactions of the amine **1** with various *para*- and *meta*-substituted iodobenzenes provided good to high yields of the products **99**–**114** (63–83%). The influence of the electron properties of the substituents was poorly manifested though the yields in the reactions with the electron donors *p*-iodotoluene and *p*-iodoanisole, and these were among the smallest (63–64%). DMSO also helped to carry out the reactions with much more problematic *ortho*-substituted iodobenzenes (R = Me, F, Cl, CN). Further, 2-iodotoluene, taken in a three-fold excess, gave a 66% yield of the arylation product **115**, while other *o*-substituted iodobenzenes provided 47–48% yields of the corresponding compounds **116**–**118**.



85: n = 1
86: n = 0

87: n = 1, R = H, 66% (L2)
88: n = 1, R = Ph, 50% (L1)
89: n = 1, R = F, 57% (L1)
90: n = 1, R = CF_3, 52% (L2)
91: n = 1, R = CH_3, 70% (L1)
92: n = 1, R = OCH_3, 79% (L1)
93: n = 0, R = H, 84% (L2)
94: n = 0, R = Ph, traces (L2)
95: n = 0, R = F, 41% (L2)
96: n = 0, R = CF_3, 20% (L2)
97: n = 0, R = CH_3, 28% (L2)
98: n = 0, R = OCH_3, 35%

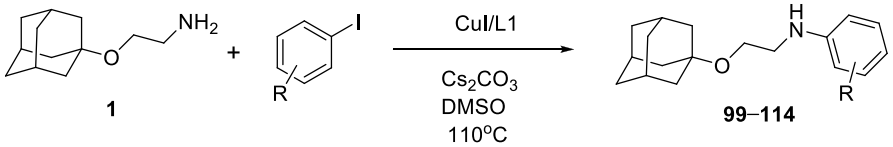
Scheme 4. CuI-catalyzed *N*,*N*′-diarylation of the adamantane-containing diamines with iodobenzenes.



1, 3–5, 28, 29, 34, 35

6, 8–10, 45, 49, 66, 67

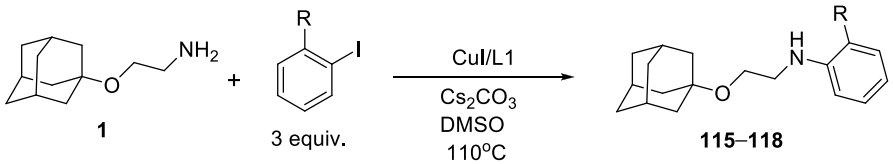
6: X = 1-(OCH_2CH_2), 76%
8: X = 2-(CH_2CH_2), 67%
9: X = 1-CH_2, 72%
10: X = 1-($CH_2CH(CH_3)$), 60%
45: X = 2-($CH(CH_3)CH_2$), 68%
49: X = 2-($CH(C_2H_5)CH_2$), 65%
66: X = 1-($CH(CH_3)$), 62%
67: X = 1-(CH(Ph)), 31%



1

99–114

99: R = 4-Br, 74%
100: R = 3-Br, 72%
101: R = 3-Cl, 66%
102: R = 4-Me, 63%
103: R = 3-Me, 76%
104: R = 4-OMe, 64%
105: R = 3-OMe, 83%
106: R = 4-CN, 78%
107: R = 3-CN, 79%
108: R = 4-MeCO, 74%
109: R = 3-MeCO, 66%
110: R = 4-COOEt, 75%
111: R = 3-COOEt, 77%
112: R = 4-Ph, 69%
113: R = 3-Ph, 66%
114: R = 4-COPh, 75%



1

3 equiv.

115–118

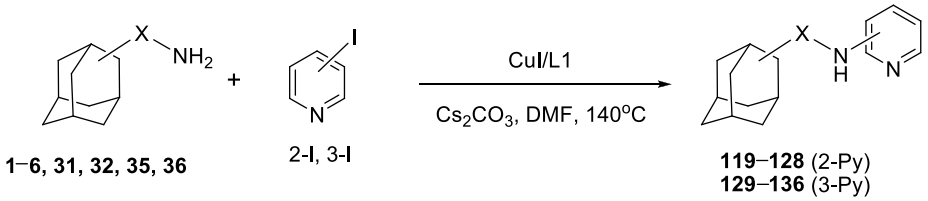
115: R = Me, 66%
116: R = F, 47%
117: R = Cl, 48%
118: R = CN, 48%

Scheme 5. CuI-catalyzed *N*-arylation of the adamantane-containing amines with iodobenzenes–effect of DMSO.

3. CuI-Catalyzed Heteroarylation of Adamantane-Containing Amines

Molecules which combine adamantane and pyridine moieties in their structure are of great importance due to their versatile biological activities. A 2-aminoadamantyl-containing derivative of pyrrolopyridine known as Peficitinib is used for rheumatoid arthritis treatment [90], and Cu(II) complexes of certain adamantane-substituted pyridines possess anticancer activity [91]. Derivatives of 2-aminopyridine with adamantane fragments were shown to inhibit 11β-hydrosteroid dehydrogenase 11β-HSD1 [92–94], and adamantane derivatives of three-substituted pyridine act as antifungal [95] and antinicotinic [96] agents. A great variety of methods exists to introduce heteroaromatic moieties in the adamantane-containing compounds. Interesting radical reactions for the direct transformations of adamantane have been described in a recent review [97]. Thus, quinolinyl-substituted adamantane was obtained via a radical process [98], and modern photocatalytic [99] and photoredox [100] processes were applied for the introduction of quinoline and trifluoromethylpyridine structural fragments into adamantane moiety.

We investigated the possibilities of the Cu(I)-catalyzed amination of 2- and 3-iodopyridines (Scheme 6). Ligands L1-L4 were tested and the best efficiency of L1 was undoubtedly shown. The reactivity of 2-iodopyridine was compared with that of 2-bromopyridine, and while the first afforded a 72% yield in the reaction with the amine **1**, the latter provided 57% of the *N*-pyrid-2-yl containing product **119**. A series of the adamantane-containing amines was tested in the reaction with 2-iodopyridine, and those with the unhindered amino group provided good to high yields of the target products (55–90%) [101]. In the case of the more sterically demanding amines **4** and **5**, the use of three equiv. of PhI was necessary to increase the yields of **123** and **124**; the more hindered amines **35** and **36** provided low yields of the corresponding products **127** and **128** (15 and 36%, respectively).



1–**6**, **31**, **32**, **35**, **36**

2-**I**, 3-**I**

119–**128** (2-Py)
129–**136** (3-Py)

2-Py

119: X = 1-(OCH_2CH_2), 72%
120: X = 1-(CH_2CH_2), 90%
121: X = 2-(CH_2CH_2), 90%
122: X = 1-CH_2, 63%
123: X = 1-($CH_2CH(CH_3)$), 57% (3 equiv. 2-IPy)
124: X = 2-($CH(CH_3)CH_2$), 90% (3 equiv. 2-IPy)
125: XNH_2 = 2-NH_2, 55%
126: X = 2-(piperazin-4-yl), 55%
127: X = 1-(CH(Ph)), 15%
128: XNH_2 = 1-NH_2, 36%

3-Py

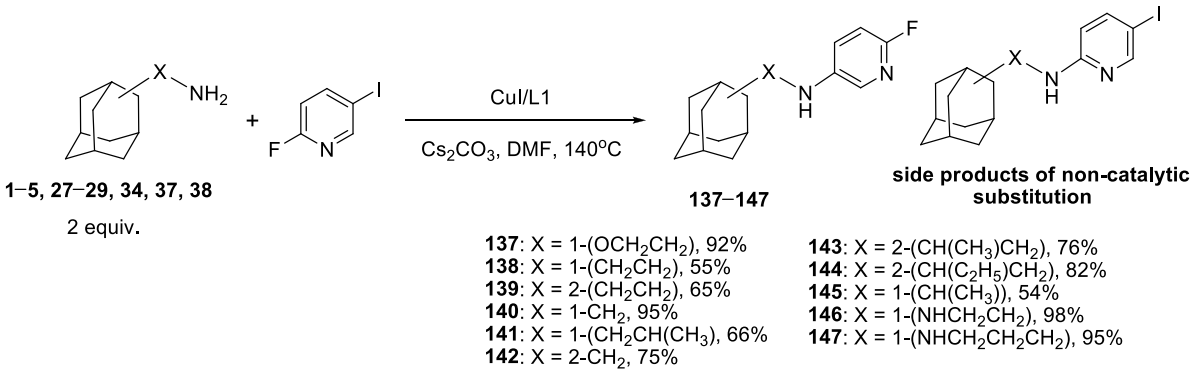
129: X = 1-(OCH_2CH_2), 74%
130: X = 1-(CH_2CH_2), 83%
131: X = 2-(CH_2CH_2), 85%
132: X = 1-CH_2, 75% (3 equiv. 3-IPy)
133: X = 1-($CH_2CH(CH_3)$), 75% (3 equiv. 3-IPy)
134: X = 2-($CH(CH_3)CH_2$), 73%
135: XNH_2 = 2-NH_2, 67%
136: X = 2-(piperazin-4-yl), 55% (3 equiv. 3-IPy)

Scheme 6. CuI-catalyzed *N*-heteroarylation of the adamantane-containing amines with 2- and 3-iodopyridines.

Similar results were obtained with 3-iodopyridine (Scheme 6). Amines **1**–**3**, **28**, and **31** afforded 67–85% yields of the *N*-heteroarylated products and, in the case of the more sterically hindered amines **4** and **5**, the application of three equiv. of PhI was required to increase the yields of compounds **132**, **133**. To note, the secondary cyclic amino group in the piperazinyl derivative of adamantane **32** turned out to be less reactive than the primary amino groups, and it also demanded the use of PhI excess.

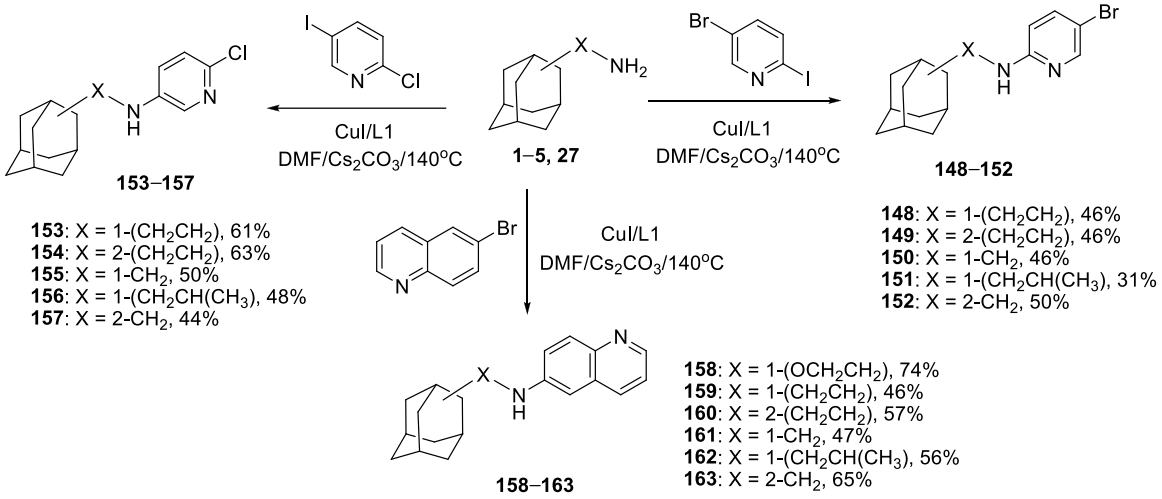
As a special case, we studied the amination of 2-fluoro-5-iodopyridine with a series of adamantane-containing amines (Scheme 7) [102]. The main peculiarity of this process is the competition of the Cu(I)-catalyzed substitution of the iodine atom and the non-catalytic substitution of the fluorine atom. In the case of the application of 10 mol% catalyst and 1:1 ratio of the reagents, generally, only the mixtures of the products were obtained, but the

use of 20 mol% catalyst and two-fold amount of the amine led to a substantial increase in the yields of the target 5-amino-2-fluoropyridines. In some cases (compounds **137**, **140**, **146**, and **147**), they reached 92–98%, and it is noteworthy that enough reluctant amines such as **34** and **37** successfully participated in this reaction.



Scheme 7. CuI-catalyzed *N*-heteroarylation of the adamantane-containing amines with 2-fluoro-5-iodopyridne.

The amines **1–5** and **27** were introduced in the reactions with other dihalopyridines to explore the selectivity of the iodine substitution (Scheme 8). The reactions with 2-bromo-5-iodopyridine turned out to be totally non-selective, and the amination of the isomeric 5-bromo-2-iodopyridine led to the corresponding products of the iodine substitution **148–152** in moderate yields (31–50%). The amination of 2-chloro-5-iodopyridine with the same amines produced compounds **153–157** in somewhat higher yields (44–63%). Nevertheless, the presence of much-less reactive additional halogen atoms (Cl, Br) diminished the selectivity of the amination process, giving rise to unidentified by-products.



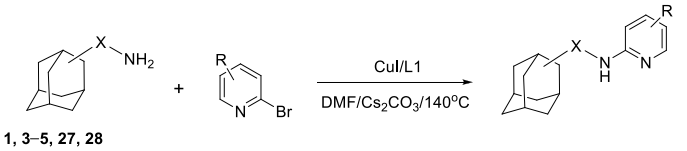
Scheme 8. CuI-catalyzed *N*-heteroarylation of the adamantane-containing amines with 5-bromo-2-iodopyridine, 2-chloro-5-iodopyridine, and 6-bromoquinoline.

Though 3-bromopyridine was found to be unreactive in Cu(I)-catalyzed amination, 6-bromoquinoline was successfully aminated by a series of adamantane-containing amines, and the yields of the products **158–163** varied from 46 to 74%. In all of the abovementioned processes, the CuI/L1 catalytic system was the most efficient.

It is well known that the adamantane derivatives bearing fluorine substituents are of substantial interest for a drug design. Indeed, compounds combining adamantane and fluoroaryl moieties display antituberculosis [103] and antiinflammatory [104] activities, as they inhibit tropoisomerase II [105] and purino receptor P2RX7 [106]. Adamantane deriva-

tives with trifluoromethyl substituent inhibit 11β-HSD1 [93,107], melanin concentrating hormone MHC1 [108], and the ligands of cannabinoid receptor CB2 [109].

In this regard, we studied the heteroarylation of several adamantane-containing amines, **1**, **3**–**5**, **27**, and **28**, with fluoro- and triflurormethyl-substituted 2-bromopyridines [110,111]. The reactions were run with 2-bromo-3-fluoro-, 5-fluoropyridines, and 3-, 4-, 5-, and 6-trifluoromethylsubstituted 2-fluoropyridines using the optimized CuI/L1 catalytic system (Scheme 9). It was found that 2-bromo-3-fluoropyridine and especially 2-bromo-3-trifluoromethylpyrdine were not reactive enough under copper catalysis conditions due to steric hindrances at the bromine atom; thus, they were aminated using alternative Pd(0)-catalyzed reactions. The other 2-bromopyridines allowed for good to high yields of the corresponding products. The best results were obtained with the amine **3**, as it produced *N*-pyridyl derivatives **165**, **171**, **177**, and **183** in 79–89% yields. Among the CF_3 derivatives, 2-bromo-6-trifluoromethylpyridine allowed for the formation of the amination products in the highest yields (up to 97% in the case of **186**). Probably, the reactivity of the bromine atom in this compound was optimal: on one hand, enough for the amination reaction to proceed at a sufficient rate, on the other hand, allowing for avoidance of the formation of many by-products in the course of other catalytic processes.



1, 3–5, 27, 28

R = 5-F	R = 4-CF_3	R = 5-CF_3	R = 6-CF_3
164: X = 1-(OCH_2CH_2), 66%	**170**: X = 1-(OCH_2CH_2), 62%	**176**: X = 1-(OCH_2CH_2), 65%	**182**: X = 1-(OCH_2CH_2), 58%
165: X = 2-(CH_2CH_2), 84%	**171**: X = 2-(CH_2CH_2), 79%	**177**: X = 2-(CH_2CH_2), 81%	**183**: X = 2-(CH_2CH_2), 89%
166: X = 1-CH_2, 61%	**172**: X = 1-CH_2, 46%	**178**: X = 1-CH_2, 59%	**184**: X = 1-CH_2, 49%
167: X = 1-($CH_2CH(CH_3)$, 67%	**173**: X = 1-($CH_2CH(CH_3)$, 56%	**179**: X = 1-($CH_2CH(CH_3)$, 53%	**185**: X = 1-($CH_2CH(CH_3)$, 67%
168: X = 2-CH_2, 75%	**174**: X = 2-CH_2, 64%	**180**: X = 2-CH_2, 69%	**186**: X = 2-CH_2, 97%
169: X = 2-($CH(CH_3)CH_2$), 65%	**175**: X = 2-($CH(CH_3)CH_2$), 52%	**181**: X = 2-($CH(CH_3)CH_2$), 71%	**187**: X = 2-($CH(CH_3)CH_2$), 69%

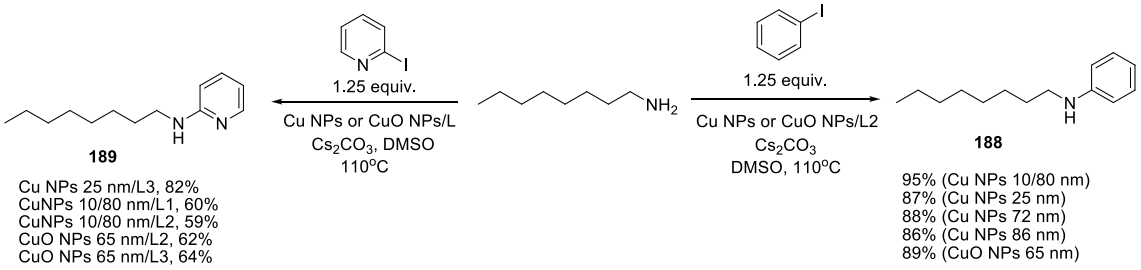
Scheme 9. CuI-catalyzed *N*-heteroarylation of the adamantane-containing amines with fluoro- and trifluoromethyl-substituted 2-bromopyridines.

4. C-N Bond Formation Using Unsupported Copper Nanoparticles

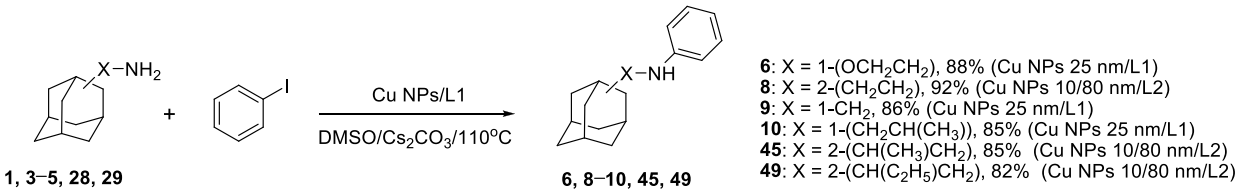
A special case is the use of copper nanoparticles (Cu NPs) in catalytic C–N bond formation. Often, copper and copper oxide nanoparticles immobilized on various supports are used, such as nanocatalysts immobilized on silica gel [112] and maghemite-silica magnetic support [113]; the following supports are also well-known: TiO_2 [114], graphene [115], and multiwall carbon nanotubes (MWCNTs) [116]. The use of unsupported copper nanoparticles in amination reactions is quite rare, and mainly CuO NPs were described for this purpose [117–121].

We began an investigation of the possibilities of the unsupported copper and copper oxide nanoparticles to promote the arylation of various amines, including adamantane-containing compounds. At first, the optimal conditions for the Cu-catalyzed amination of PhI with a model *n*-octylamine were established (Scheme 10) using copper nanoparticles of various average sizes: 10/80 nm (mixture of two fractions), 25 nm, 72 nm, 86 nm, and CuO 65 nm [122,123]. The reactions were run in DMSO or DMF at 110 °C or 140 °C, and a variety of ligands were tested. For the arylation with iodobenzene, L2 was found to be the best choice, as it allowed for the synthesis of *N*-octylaniline **188** in 86–95% yields. The best result (82%) for the heteroarylation of *n*-octylamine with 2-iodopyridine was obtained using the Cu NPs 25 nm/L3 catalytic system, and other combinations of nanoparticles and ligands gave poorer yields. The possibilities of the catalyst recycling were revealed to be strongly dependent on the copper source, and the best result was obtained with the Cu NPs 25 nm/L1 system (up to eight cycles without loss of the catalyst's activity).

Optimized conditions were applied to the arylation of a variety of adamantane-containing amines, **1**, **3**–**5**, **28**, and **29**, with iodobenzene (Scheme 11) [89].

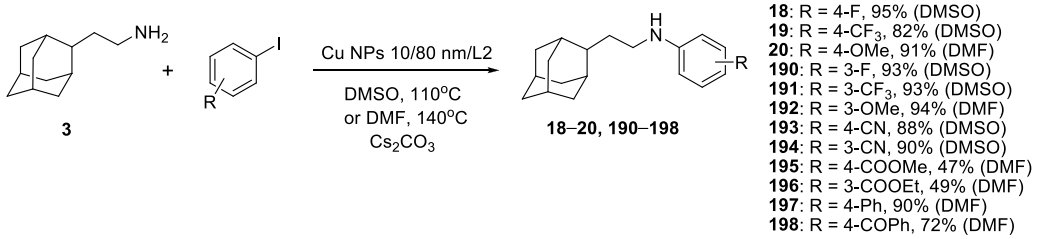


Scheme 10. Initial studies of the (hetero)arylation of a model *n*-octylamine with iodobenzene and 2-iodopyridine using unsupported Cu and CuO nanoparticles.



Scheme 11. *N*-arylation of the adamantane-containing amines with iodobenzene using unsupported Cu NPs.

The results were encouraging, as the yields of the target products (85–92%) were substantially higher than those obtained with CuI catalyst (65–76%, Scheme 5). The application of various substituted iodobenzenes for the arylation of amine **3** in the presence of another efficient system Cu NPs 10/80 nm/L2 (Scheme 12) was equally successful, and the yields of many products reached 90% and more (**18**, **20**, **190**–**192**, **194**, and **197**). Some of these reactions gave better results in DMSO at 110 °C, and others successfully proceeded in DMF at 140 °C. It is clearly seen that the high yields could be obtained both with electron donor and electron withdrawing substituents in iodobenzenes. The experiments on catalyst recycling demonstrated the possibility of the use of Cu NPs 25 nm/L1 for the arylation of amine **3** with iodobenzene at least in seven cycles without a decrease in the product's yield.

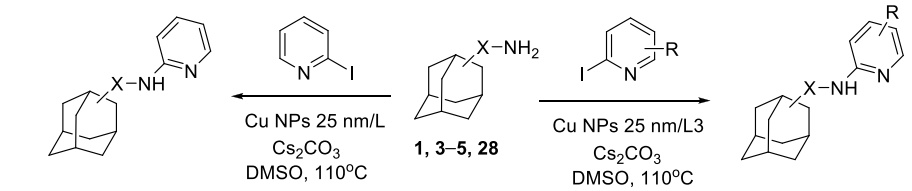


Scheme 12. *N*-arylation of the adamantane-containing amine **3** with substituted iodobenzenes using unsupported Cu NPs.

The *N*-heteroarylation of the adamantane-containing amines turned out to be more problematic (Scheme 13) [124]. The reactions of the amines **1**, **3**–**5**, and **28** with 2-iodopyridine gave 62–76% yields and it was noted that the effect of the ligand (L1 or L3) was dependent on the structure of the amine. In the reactions with the fluorine-containing 2-bromopyridines, the Cu NPs 25 nm/L3 catalytic system was found to be the best; however, the yields of the products ranged from humble, 24% (**166**), to high, 75–78% (**183**, **184**). Generally, as in the reactions catalyzed by CuI/L1, the best results were obtained with 2-bromo-6-trifluoromethylpyridine.

While copper nanoparticles were more efficient than CuI in the *N*-arylation of the adamantane-containing amines with iodoarenes, they provided lower yields with bromoarenes under the same conditions, e.g., the attempts to introduce 6-bomoquinoline in the amination with several amines in the presence of Cu NPs/L1 resulted in 11–25% yields of the corresponding products **158**, **160**, and **161**, while these reactions catalyzed by

the CuI/L1 system provided 47–74% yields (Scheme 8). However, the application of Cu NPs/L2 for these reactions provided stable 70–75% yields of the products.



119: X = 1-(OCH_2CH_2), 69% (L1)
121: X = 2-(CH_2CH_2), 76% (L3)
122: X = 1-CH_2, 64% (L3)
123: X = 1-($CH_2CH(CH_3)$), 73% (L3)
124: X = 2-($CH(CH_3)CH_2$), 62% (L1)

165: X = 2-(CH_2CH_2), R = 5-F, 39%
166: X = 1-CH_2, R = 5-F, 24%
171: X = 2-(CH_2CH_2), R = 4-CF_3, 54%
177: X = 2-(CH_2CH_2), R = 5-CF_3, 62%
178: X = 1-CH_2, R = 5-CF_3, 42%

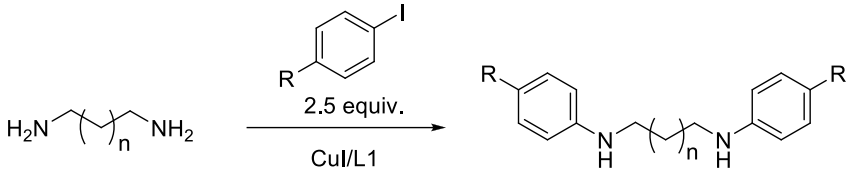
183: X = 2-(CH_2CH_2), R = 6-CF_3, 78%
184: X = 1-CH_2, R = 6-CF_3, 75%
185: X = 1-($CH_2CH(CH_3)$), R = 6-CF_3, 41%
186: X = 2-($CH(CH_3)CH_2$), R = 6-CF_3, 66%
199: X = 2-($CH(C_2H_5)CH_2$), R = 6-CF_3, 61%

Scheme 13. *N*-heteroarylation of the adamantane-containing amines with substituted iodopyridines using unsupported Cu NPs.

5. *N,N′*-Diarylation of the Di- and Polyamines Using Cu(I) Catalysis

Naturally occurring diamines such as putrescine **201**, cadaverine **202**, and some polyamines, are biologically active compounds which play a key role in cells' proliferation and apoptosis [125], and more and more attention is attracted to their *N*-aryl derivatives [126–128], E.g., such derivatives of putrescine and cadaverine showed cytotoxic and antiproliferative activity [129], *N*-(*p*-tolyl) substituted cadaverine, and hexane-1,6-diamine demonstrated an affinity to NMDA receptors and antileishmaniasis activity [130,131].

We were mainly interested in the synthesis of *N,N′*-diarylsubstituted diamines and, for this purpose, conducted a series of reactions of the diamines **200–203** with iodobenzene and some *p*-substituted derivatives (Scheme 14) [132]. The catalytic system CuI/L1 was shown to be optimal and the yields of the reaction products **204–207** reached 70–80% in the best cases. It was noted that the electron-enriched *p*-iodoanisole was less reactive, giving 20–50% yields of the target compounds **204e–207e**; on the contrary, the reactions with electron-deficient 4-iodobenzotrifluoride provided enough high yields of the compounds **204d–207d**.



200: n = 1
201: n = 2
202: n = 3
203: n = 4

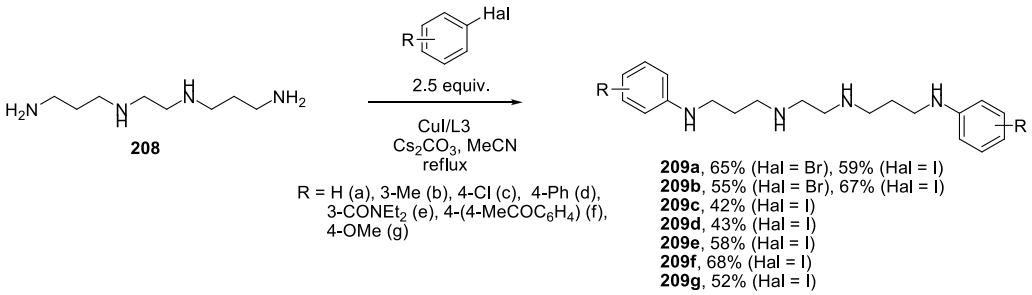
204a–e: n = 1, 42–75%
205a–e: n = 2, 46–58%
206a–e: n = 3, 22–53%
207a–e: n = 4, 34–81%

Scheme 14. CuI-catalyzed *N,N′*-diarylation of the diamines **200–203** with substituted iodobenzenes.

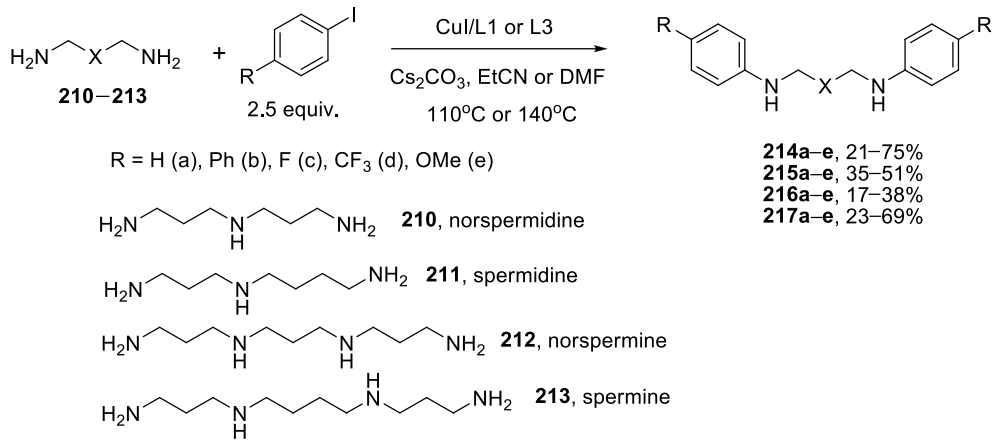
The investigation of the *N,N′*-diarylation of the tatraamine **208** with iodobenzene and a number of aryl iodides revealed that the best ligand in this case was L3 with MeCN as a solvent (Scheme 15) [133]. Bromobenzene was shown to be equally reactive with this tetraamine, which could be due to the coordination of copper to the tetraamine, resulting in a higher reactivity of the catalytic species. On the other hand, it caused the side reaction of the *N*-arylation of the secondary amino groups in the tetraamine, and moderate to good yields of the target compounds **209a–g** (42–67%) were obtained independently of the electron properties of the substituents in iodobenzenes.

Further, several iodobenzenes were introduced in the reactions with the naturally occurring tri- and tetra-amines **210–213** (Scheme 16). The yields of the target *N,N′*-diaryl derivatives **214–217** varied substantially depending on the nature of the polyamines and substituents in the aryl iodides. To note, in the case of **210** and **212**, containing only

trimethylenediamine moieties, the CuI/L3/EtCN catalytic system was more efficient, while in the reactions of **211** and **213** with tetramethylenediamine fragments, CuI/L1/DMF was found to act better. Again, *p*-iodoanisole provided the lowest yields of the target compounds, and the *N*,*N*′-diarylation of **210** and **213** generally proceeded more smoothly and resulted in higher yields of the products compared to the two other polyamines.



Scheme 15. CuI-catalyzed *N*,*N*′-diarylation of the tetraamine **208** with substituted halobenzenes.

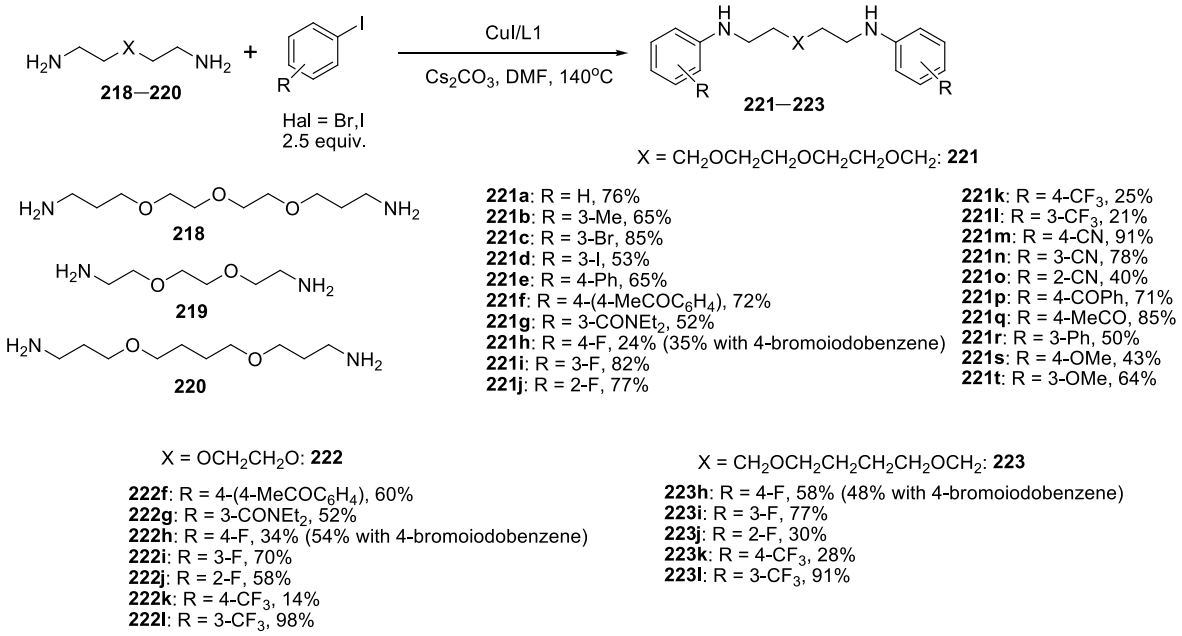


Scheme 16. CuI-catalyzed *N*,*N*′-diarylation of the tri and tetra-amines **210**–**213** with substituted iodobenzenes.

Oxadiamines, due to their hydrophilicity and chelating ability, are employed as flexible linkers for the synthesis of biologically active compounds. The structure and the length of the linker can modify the activity [134], and linkers can be incorporated in the organic molecules [135–138] or serve as a bidentate ligand for binding two Pd or Pt complexes [139].

We investigated the *N*,*N*′-diarylation of three different oxadiamines, **218**–**220**, varying their length, and number of oxygen atoms and methylene groups between N and O atoms (Scheme 17) [140]. CuI/L1 in DMF was shown to be the most active catalytic system, and trioxadiamine **218** was reacted with a large series of aryl iodides. In the majority of cases, the yields were good to high, attaining 91% in the case of **221m** (with 4-CN substituent in the phenyl ring). A lower, 43%, yield was recorded for the product **221s**, obtained from the electron-enriched *p*-iodoanisole, and, suddenly, the reactions with *p*-fluoroiodobenzene and 4-iodobenzotrifluorides gave very small yields of the target compounds **221h,k**. Similar observations were true for the two other oxadiamines, **219** and **220**, which also encountered difficulties upon reacting with these aryl iodides, especially with the latter one. On the contrary, much higher yields were observed in the reactions with *o*-fluoroiodonbenzene (77% yield of **221j** and 58% yield of **222j**).

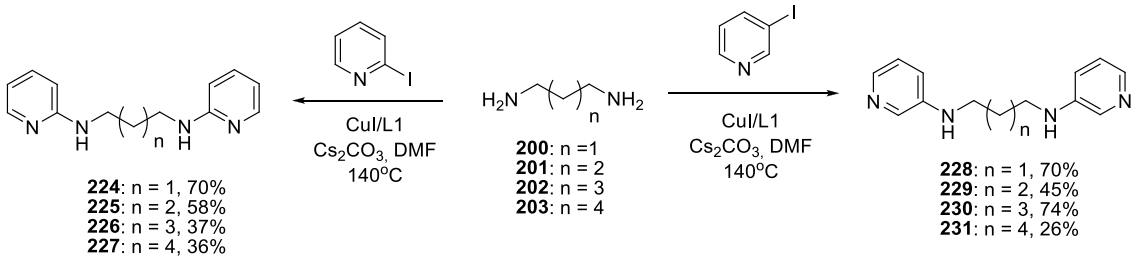
Special investigations were also carried out to verify the absence of the side *N*,*N*-diarylation process, which is common for palladium-catalyzed amination reactions. For this purpose, diamines and oxadiamines were reacted with 10 equiv. of PhI and only the traces of the polyarylated derivatives were detected in the reaction mixtures in several cases. On the other hand, it helped to increase the yields of some *N*,*N*′-diphenyl derivatives to 80–90%.



Scheme 17. CuI-catalyzed *N*,*N*′-diarylation of the oxadiamines **218**–**220** with substituted iodobenzenes.

6. *N*,*N*′-Diheteroarylation of Di- and Polyamines Using Cu(I) Catalysis

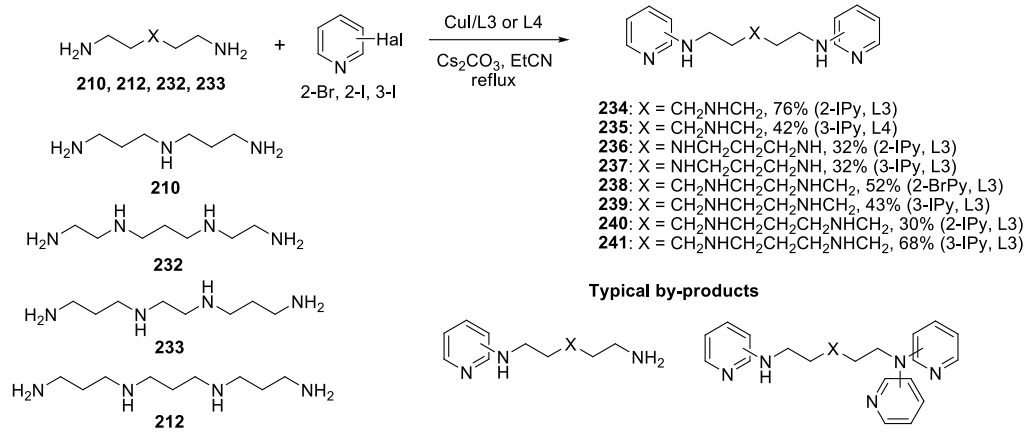
The next part of our research was dedicated to the N,N′-heteroarylation of the di- and poly-amines. The diamines **200**–**203** reacted with 2- and 3-iodopyridines in the presence of the CuI/L1 catalytic system, and the yields of the target dipyridinyl derivatives were dependent on the nature of the diamines and were the highest for the shortest diamine (compounds **224** and **228**) (Scheme 18) [141]. The use of 20 mol% catalyst was crucial for the *N*,*N*′-diheteroarylation; however, in many cases, monopyridinyl derivatives were also isolated.



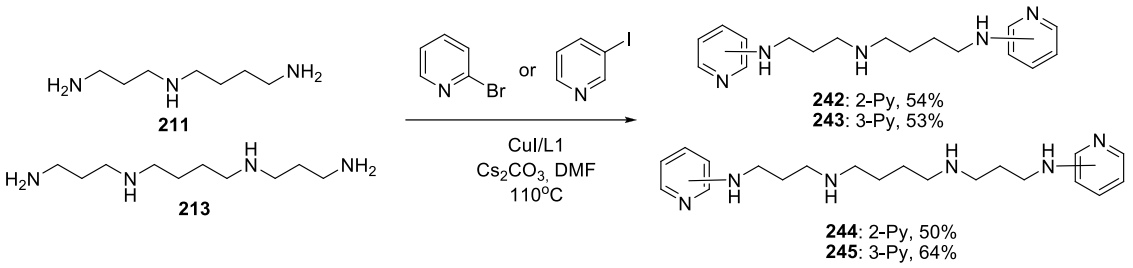
Scheme 18. CuI-catalyzed N,N′-diheteroarylation of the diamines **200**–**203** with 2- and 3-iodopyridines.

More complicated were the reactions of tri- and tetraamine **210**, **212**, **232**, and **233** with 2- and 3-iodopyridines due to many side reactions such as the heteroarylation of the secondary amino group and the *N*,*N*-diheteroarylation of the primary amino group (Scheme 19) [142].

In several cases, the formation of great amounts of monopyridinyl derivatives was observed. Almost in every case, the adjustment of the catalytic system was needed, including the ligands (L3 or L4), the catalyst loading, and a proper choice between 2-iodopyridine and less-active 2-bromopyridine. As a result, it was possible to obtain the *N*,*N*′-di(pyridine-2-yl) derivative of the triamine **234** and the *N*,*N*′-di(pyridine-3-yl) derivative of the tetraamine **241** in good yields (76 and 68%, respectively), while other products, **235**–**240**, were isolated in moderate yields: 30–52%. Spermidine **211** and spermine **213** reacted better with 2-bromopyridine and 3-iodopyridine, providing 50–64% yields of **242**–**245** (Scheme 20), but they demanded the application of the another catalytic system, i.e., CuI/L1/DMF, due to their lower reactivity, probably due to the presence of the tetramethylenediamine moieties [141].

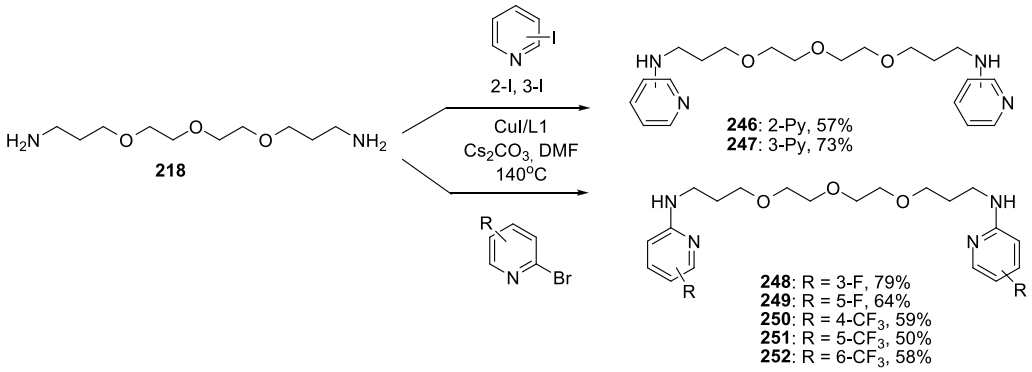


Scheme 19. CuI-catalyzed *N*,*N*′-diheteroarylation of the tetraamines **210**, **212**, **232**, and **233** with 2- and 3-iodopyridines.



Scheme 20. CuI-catalyzed *N*,*N*′-diheteroarylation of the naturally occurring triamine **211** and tetraamine **213** with 2- and 3-iodopyridines.

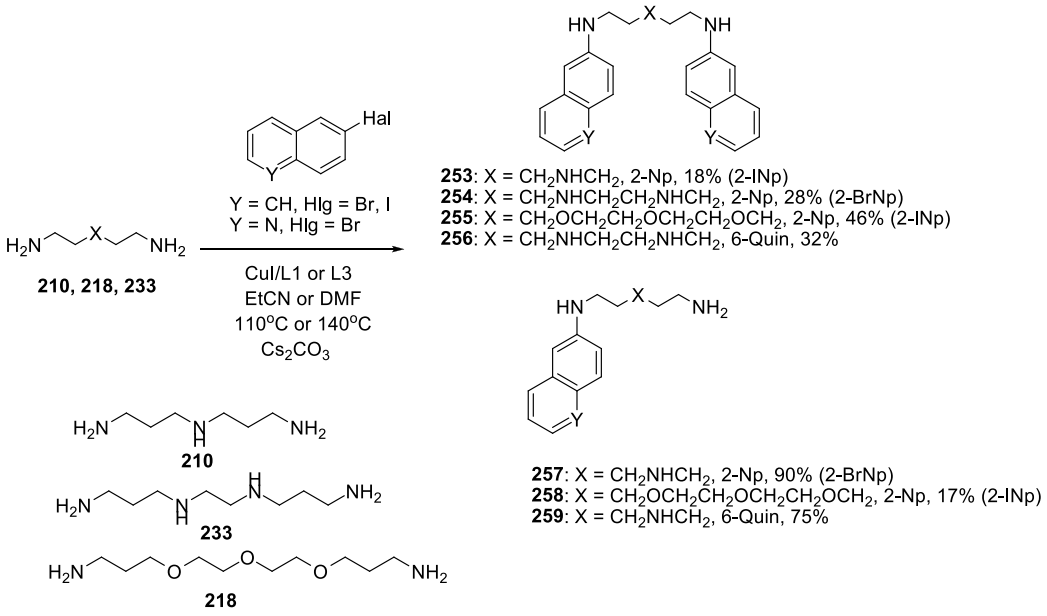
The N,N′-diheteroarylation of the trioxadiamine **218** with 2- and 3-iodopyridines as well as fluoro- and trifluoromethylsubstituted 2-bromopyridine was successful in the presence of CuI/L1 (Scheme 21), giving good to high yields of the desired compounds. Notable is the 79% yield of the compound **248**, the product of the reaction with 2-bromo-3-fluropyridine; in this case, the substitution at the *ortho*-position was unexpectedly very efficient.



Scheme 21. CuI-catalyzed *N*,*N*′-diheteroarylation of the trioxadiamine **218** with 2- and 3-iodopyridines and substituted 2-bromopyridine.

The possibility of introducing simple fluorophore groups such as naphthalene and quinoline in the polyamines was shown using several exemplary reactions (Scheme 22) [143]. Triamine **210** reacted with 2-iodonaphthalene to give only an 18% yield of the target diaryl derivative **253**, while tetraamine **233** was able to produce the corresponding compound **254** in a 28% yield using less-active 2-bromonaphthalene. Note that the reaction of **210** with 2-bromonaphthalene afforded only monoaryl derivative **257** in 90% yields and the reac-

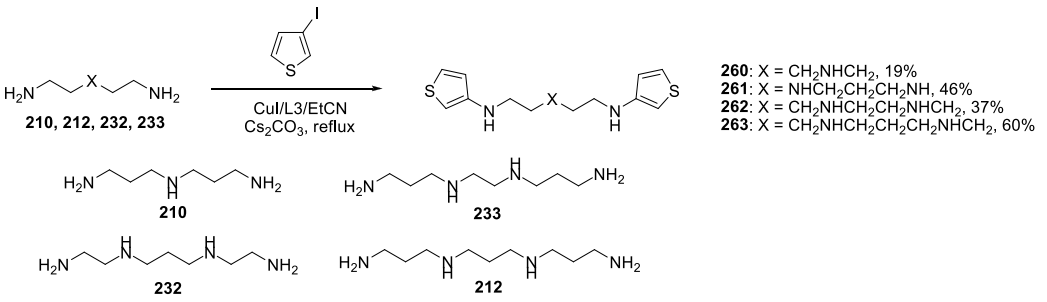
tion of the tetraamine **233** with a more active 2-iodonaphthalene was totally non-selective. Similar results were obtained when reacting tri- and tetra-amines with 6-bromoquinoline (formation of monoquinolinyl derivative of the triamine **259** and *N*,*N*′-diquinolinyl derivative of the tetraamine **256**). These facts demonstrate a strong dependence of the reactivity of polyamines on the number of ethylenediamine and trimethylenediamine fragments in their structure, as well as on the activity of (hetero)aryl halides.



Scheme 22. CuI-catalyzed *N*,*N*′-di(hetero)arylation of the polyamines **210**, **218**, and **233** with 2-bromo- and 2-iodonaphthalenes and 6-bromoquinoline.

Trioxadiamine **218** was less active and helped to produce its *N*,*N*′-dinaphthyl derivative **255** in a higher yield (46%) using 2-iodonaphthalene.

The reactions of the triamine **210** and several tetraamines **212**, **232**, and **233** with 3-iodothiophene were run in the presence of CuI/L3 in boiling EtCN, and the yields of the desired *N*,*N*′-diheteroaryl derivatives **260**–**263** were also strongly dependent on the nature of the starting polyamines (Scheme 23) [144]. The highest yield (60%) was obtained with the tetraamine **212**, possessing only trimethylenediamine moieties.

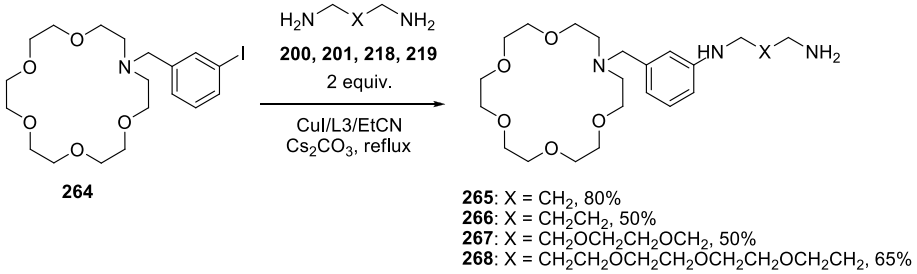


Scheme 23. CuI-catalyzed *N*,*N*′-di(hetero)arylation of the polyamines with 3-iodothiophene.

7. Copper-Catalyzed Amination in the Modifications of the Aza- and Diazacrown Ethers

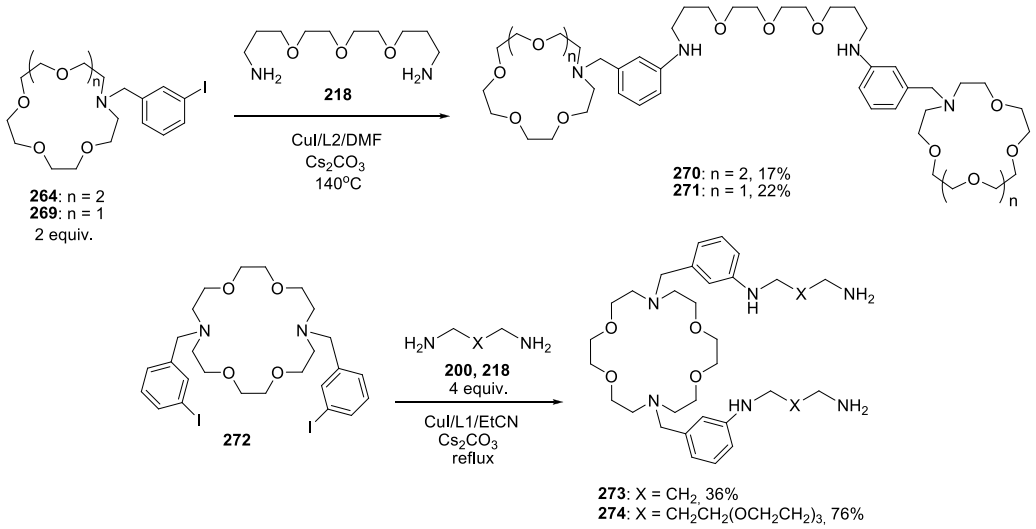
Our investigations of the synthesis of the macrocycles definitely showed that copper catalysis is not applicable to this process, as all macrocyclization reactions require diluted enough conditions and Cu-catalyzed amination normally proceeds at 0.25–0.5 M concentrations of the reagents. However, it can be used for some modifications of the macrocycles possessing iodobenzyl substituents. It was shown to be possible to synthesize diamino

derivatives of the azacrown ethers using this approach (Scheme 24). The reactions of *N*-(3-iodobenzyl)-substituted 1-aza-18-crown-6 **264** were successfully aminated with the excess of the diamines **200** and **201**, and the oxadiamines **218** and **219** to give the corresponding derivatives **265**–**268** in 50–80% yields [145].



Scheme 24. CuI-catalyzed amination of 3-iodobenzyl-substituted 1-aza-18-crown-6 ether **264**.

Note that the isomeric *N*-(4-iodobenzyl) derivative was much less reactive and provided 20% or less yields of the monoamination products. This method can be employed in the synthesis of bismacrocyclic compounds with the trioxadamine linkers **270** and **271**; in this case the excess of azacrown derivatives should be used (Scheme 25). Also, the diamination of the *N*,*N*′-di(3-iodobenzyl) derivative of diazacrown **272** was carried out using an excess of propane-1,3-diamine **200** and trioxadiamine **218**, with the yields of the corresponding products **273** and **274** being 36 and 76%, respectively.



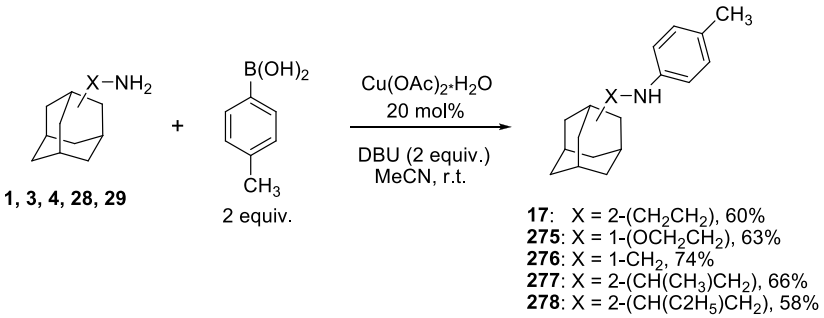
Scheme 25. CuI-catalyzed *N*,*N*′-diarylation and diamination of the derivatives of the aza- and diazacrown ethers.

The attempts to apply the analogous reactions to the iodobenzyl derivatives of porphyrins were not successful and the introduction of the diamine and oxadiamine moieties in these compounds could be achieved only using Pd-catalyzed amination reactions [146].

8. Chan-Lam Reactions for the Arylation of Adamantane-Containing Amines, Diamines and Oxadiamines

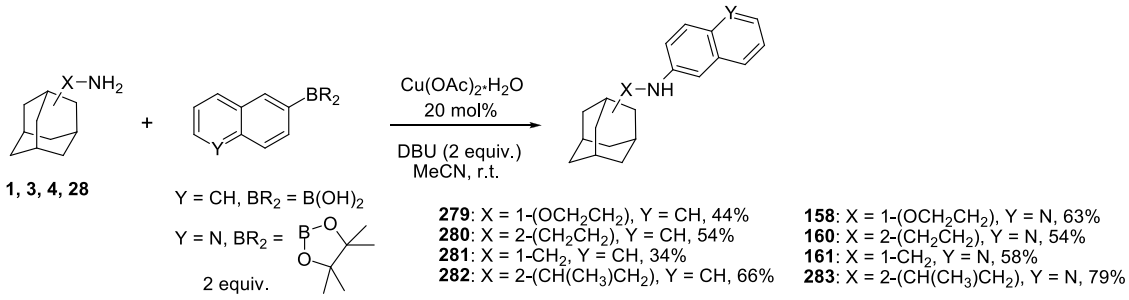
At the present time, the amines' arylation with arylboronic acids and their derivatives known as the Chan–Lam reaction has been developed steadily [147], and we also explored this alternative to arylation with aryl halides. At first, we optimized the reaction conditions using a model *p*-tolylboronic acid in the reactions with various adamantane-containing amines (Scheme 26). Standard copper (II) acetate in MeCN in the presence of DBU (2 equiv.)

and the use of *p*-tolylboronic acid excess were found to provide the highest yields. They ranged from 58 to 74% for the N-tolyl derivatives **17**, **275**–**278**.



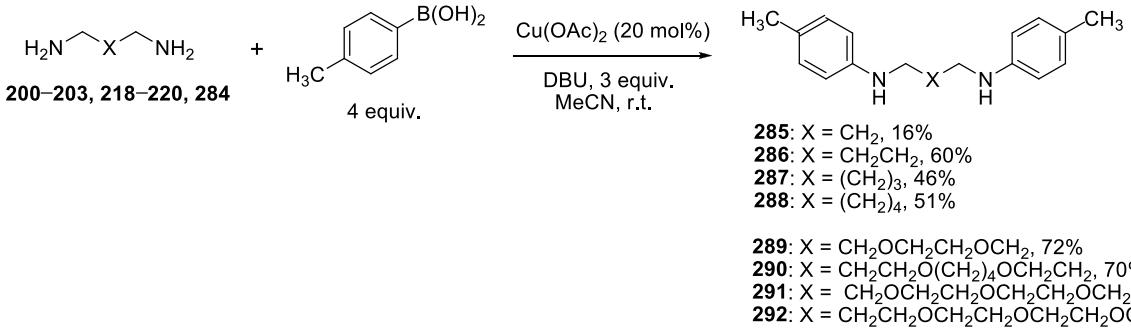
Scheme 26. Chan–Lam *N*-arylation of the adamantane-containing amines with the model *p*-tolylboronic acid.

The possibility of introducing naphthalene and quinoline moieties in the adamantane-containing amines using this method was also shown (Scheme 27). The reactions with 2-naphthalenelboronic acid gave 34–66% yields of the corresponding derivatives **279**–**282**, while the reactions with 6-quinolinyl picolinyl borate produced the compounds **158**, **160**, **161**, and **283** in 54–79% yields.



Scheme 27. Introduction of the naphthyl and quinolinyl substituents to adamantane-containing amines via Chan–Lam reaction.

At the next step, the conditions for the *N*,*N*′-diarylation of the diamines **200**–**203** and the oxadiamines **218**–**220**, **284** were elaborated (four equiv. of *p*-tolylboronic acid and three equiv. of DBU), and the corresponding target compounds **285**–**288** and **289**–**292** were synthesized (Scheme 28) [148]. Except for the propane-1,3-diamine **200** with the shortest chain, which obviously formed an inert complex with the Cu(II) cation, the other diamines and all of the oxadiamines provided good to high yields of the *N*,*N*′-darylated products (46–80%). Thus, the Chan–Lam reaction can be judged as a valuable prospective addition to the previously developed methods for the introduction of the aryl and heteroaryl substituents in the adamantane-containing amines, diamines, and oxadiamines.



Scheme 28. *N*,*N*′-diarylation of the diamines and oxadiamines with the model *p*-tolylboronic acid.

9. Conclusions and Prospects

The results presented in this review clearly demonstrate wide possibilities of copper-catalyzed amination reactions for the synthesis of *N*-(hetero)aryl derivatives of the valuable adamantane-containing amines, diamines, oxadiamines, and polyamines. The reactions catalyzed by the most-commonly used CuI were shown to proceed in DMF at 140 °C or in DMSO at 110 °C in the presence of O,O-ligands (2-isobutirylcyclohexanone and *rac*-BINOL), in the case of the adamantane-containing amines, diamines, and oxadiamines or in the presence of N,O ligands (proline, *N*,*N*-dimethylglycine) in the case of tri- and tetra-amines. Under these conditions, iodoarenes and iodopyridines were found to be substantially more reactive than their bromosubstituted analogues, although with certain exclusions. Thus, bromobenzene and 2-bromopyridine were suitable for reactions with some polyamines, and more reactive F- and CF_3-substituted 2-bromopyridines were successfully employed in reactions with the adamantane-containing amines. The majority of the adamantane-containing amines were found to normally participate in the copper-catalyzed *N*-(hetero)arylation reactions; nevertheless, several bulky amines with enough hindered amino groups were reluctant in this process and could provide target products in normal yields only in the Pd-catalyzed amination reactions. Copper-catalyzed amination has an important advantage over its Pd-catalyzed alternative, as it does not afford *N*,*N*-diarylation products even in the presence of a great excess of the aryl halide. On the other hand, some drawbacks should be mentioned such as insufficient yields of the N,N′-diaryl compounds in certain cases due to the formation of substantial amounts of mono-derivatives. Another drawback is a possibility of the side reaction of the secondary dialkylamino group arylation in linear polyamines. At last, the reactions need concentrated solutions making macrocyclization reactions impossible.

The possibility of using commercially available Cu and CuO nanoparticles for reactions with the adamantane-containing amines has been investigated recently, and the possibility of obtaining high yields of the *N*-aryl derivatives was demonstrated. An important advantage of this approach is the possibility of reuse of the catalyst for up to seven cycles without a loss of reactivity. Further development of this method is required to engage di- and poly-amines in (hetero)arylation using copper nanoparticles. Equally, it is important to continue investigations revealing the action of nano catalysts, metal leaching during the reaction, and catalyst reusability to study the dependence of the catalyst activity on the ligands and solvents employed. This first successful syntheses of the arylated adamantane-containing amines, diamines, and oxadiamines under the conditions of the Chan–Lam reaction indicate a need to further search for its scope and limitations with our compounds and the application of the copper nanocatalysts in this process.

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References

1. Ullmann, F.; Bielecki, J. Ueber Synthesen in der Biphenylreihe. *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 2174–2185. [CrossRef]
2. Ullmann, F. Ueber eine neue Bildungsweise von Diphenylaminderivaten. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2382–2384. [CrossRef]
3. Ullmann, F.; Sponagel, P. Ueber Phenylirung von Phenolen. *Justus Liebigs Ann. Chem.* **1906**, *350*, 83–107. [CrossRef]
4. Goldberg, I. Ueber Phenylirungen bei Gegenwart von Kupfer als Katalysator. *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 1691–1692. [CrossRef]
5. Lindley, J. Tetrahedron report number 163: Copper assisted nucleophilic substitution of aryl halogen. *Tetrahedron* **1984**, *40*, 1433–1456. [CrossRef]

6. Kunz, K.; Scholz, U.; Ganzer, D. Renaissance of Ullmann and Goldberg Reactions—Progress in Copper Catalyzed C-N-, C-O- and C-S-Coupling. *Synlett* **2003**, *2003*, 2428–2439. [CrossRef]
7. Fanta, P.E. The Ullmann Synthesis of Biaryls. *Synthesis* **1974**, *1974*, 9–21. [CrossRef]
8. Tuong, T.D.; Hida, M. Mechanism of the Ullmann Condensation. I. Kinetic and Thermodynamic Studies. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 1763–1768. [CrossRef]
9. Affouard, C.; Crockett, R.D.; Diker, K.; Farrell, R.P.; Gorins, G.; Huckins, J.R.; Caille, S. Multi-Kilo Delivery of AMG 925 Featuring a Buchwald–Hartwig Amination and Processing with Insoluble Synthetic Intermediates. *Org. Proc. Res. Dev.* **2015**, *19*, 476–485. [CrossRef]
10. Ku, Y.-Y.; Chan, V.S.; Christesen, A.; Grieme, T.; Mulhern, M.; Pu, Y.-M.; Wendt, M.D. Development of a Convergent Large-Scale Synthesis for Venetoclax, a First-in-Class BCL-2 Selective Inhibitor. *J. Org. Chem.* **2019**, *84*, 4814–4829. [CrossRef]
11. Yang, Q.; Zhao, Y.; Ma, D. Cu-Mediated Ullmann-Type Cross-Coupling and Industrial Applications in Route Design, Process Development, and Scale-up of Pharmaceutical and Agrochemical Processes. *Org. Proc. Res. Dev.* **2022**, *26*, 1690–1750. [CrossRef]
12. Evendar, P.; Qu, R.-Y.; Kang, W.-M.; He, B.; Yang, G.-F. Palladium-Catalyzed Cross-Coupling Reactions: A Powerful Tool for the Synthesis of Agrochemicals. *J. Agric. Food. Chem.* **2018**, *66*, 8914–8934. [CrossRef] [PubMed]
13. Chen, J.; Yan, W.; Townsend, E.J.; Feng, J.; Pan, L.; Del Angel Hernandez, V.; Faul, C.F.J. Tunable Surface Area, Porosity, and Function in Conjugated Microporous Polymers. *Angew. Chem. Int. Ed.* **2019**, *58*, 11715–11719. [CrossRef]
14. Astridge, D.D.; Hoffman, J.B.; Zhang, F.; Park, S.Y.; Zhu, K.; Sellinger, A. Polymer Hole Transport Materials for Perovskite Solar Cells via Buchwald–Hartwig Amination. *ACS Appl. Polym. Mater.* **2021**, *3*, 5578–5587. [CrossRef]
15. Weingarten, H. Mechanism of the Ullmann Condensation. *J. Org. Chem.* **1964**, *29*, 3624–3626. [CrossRef]
16. Nicolaou, K.C.; Boddy, C.N.C.; Natarajan, S.; Yue, T.Y.; Li, H.; Bräse, S.; Ramanjulu, J.M. New Synthetic Technology for the Synthesis of Aryl Ethers: Construction of C-O-D and D-O-E Ring Model Systems of Vancomycin. *J. Am. Chem. Soc.* **1997**, *119*, 3421–3422. [CrossRef]
17. Marcoux, J.-F.; Doye, S.; Buchwald, S.L. A General Copper-Catalyzed Synthesis of Diaryl Ethers. *J. Am. Chem. Soc.* **1997**, *119*, 10539–10540. [CrossRef]
18. Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. Accelerating Effect Induced by the Structure of α-Amino Acid in the Copper-Catalyzed Coupling Reaction of Aryl Halides with α-Amino Acids. Synthesis of Benzolactam-V8. *J. Am. Chem. Soc.* **1998**, *120*, 12459–12467. [CrossRef]
19. Monnier, F.; Taillefer, M. Catalytic C–C, C–N, and C–O Ullmann-Type Coupling Reactions. *Angew. Chem. Int. Ed.* **2009**, *48*, 6954–6971. [CrossRef]
20. Beletskaya, I.P.; Cheprakov, A.V. Copper in cross-coupling reactions: The post-Ullmann chemistry. *Coord. Chem. Rev.* **2004**, *248*, 2337–2364. [CrossRef]
21. Beletskaya, I.P.; Averin, A.D. Metal-catalyzed reactions for the C(sp2)–N bond formation: Achievements of recent years. *Russ. Chem. Rev.* **2021**, *90*, 1359. [CrossRef]
22. Goodbrand, H.B.; Hu, N.-X. Ligand-Accelerated Catalysis of the Ullmann Condensation: Application to Hole Conducting Triarylamines. *J. Org. Chem.* **1999**, *64*, 670–674. [CrossRef]
23. Gujadhur, R.K.; Bates, C.G.; Venkataraman, D. Formation of Aryl–Nitrogen, Aryl–Oxygen, and Aryl–Carbon Bonds Using Well-Defined Copper(I)-Based Catalysts. *Org. Lett.* **2001**, *3*, 4315–4317. [CrossRef] [PubMed]
24. Surry, D.S.; Buchwald, S.L. Diamine ligands in copper-catalyzed reactions. *Chem. Sci.* **2010**, *1*, 13–31. [CrossRef] [PubMed]
25. Klapars, A.; Huang, X.; Buchwald, S.L. A General and Efficient Copper Catalyst for the Amidation of Aryl Halides. *J. Am. Chem. Soc.* **2002**, *124*, 7421–7428. [CrossRef] [PubMed]
26. Antilla, J.C.; Baskin, J.M.; Barder, T.E.; Buchwald, S.L. Copper–Diamine-Catalyzed N-Arylation of Pyrroles, Pyrazoles, Indazoles, Imidazoles, and Triazoles. *J. Org. Chem.* **2004**, *69*, 5578–5587. [CrossRef]
27. Ma, D.; Cai, Q.; Zhang, H. Mild Method for Ullmann Coupling Reaction of Amines and Aryl Halides. *Org. Lett.* **2003**, *5*, 2453–2455. [CrossRef]
28. Zhang, H.; Cai, Q.; Ma, D. Amino Acid Promoted CuI-Catalyzed C–N Bond Formation between Aryl Halides and Amines or N-Containing Heterocycles. *J. Org. Chem.* **2005**, *70*, 5164–5173. [CrossRef]
29. Jiang, Q.; Jiang, D.; Jiang, Y.; Fu, H.; Zhao, Y. A Mild and Efficient Method for Copper-Catalyzed Ullmann-Type N-Arylation of Aliphatic Amines and Amino Acids. *Synlett* **2007**, *2007*, 1836–1842. [CrossRef]
30. Fan, M.; Zhou, W.; Jiang, Y.; Ma, D. Assembly of Primary (Hetero)Arylamines via CuI/Oxalic Diamide-Catalyzed Coupling of Aryl Chlorides and Ammonia. *Org. Lett.* **2015**, *17*, 5934–5937. [CrossRef]
31. Gao, J.; Bhunia, S.; Wang, K.; Gan, L.; Xia, S.; Ma, D. Discovery of *N*-(Naphthalen-1-yl)-*N*′-alkyl Oxalamide Ligands Enables Cu-Catalyzed Aryl Amination with High Turnovers. *Org. Lett.* **2017**, *19*, 2809–2812. [CrossRef] [PubMed]
32. Kwong, F.Y.; Klapars, A.; Buchwald, S.L. Copper-Catalyzed Coupling of Alkylamines and Aryl Iodides: An Efficient System Even in an Air Atmosphere. *Org. Lett.* **2002**, *4*, 581–584. [CrossRef] [PubMed]
33. Jiang, D.; Fu, H.; Jiang, Y.; Zhao, Y. CuBr/rac-BINOL-Catalyzed N-Arylations of Aliphatic Amines at Room Temperature. *J. Org. Chem.* **2007**, *72*, 672–674. [CrossRef] [PubMed]
34. Shafir, A.; Buchwald, S.L. Highly Selective Room-Temperature Copper-Catalyzed C–N Coupling Reactions. *J. Am. Chem. Soc.* **2006**, *128*, 8742–8743. [CrossRef]

35. Shafir, A.; Lichtor, P.A.; Buchwald, S.L. N- versus O-Arylation of Aminoalcohols: Orthogonal Selectivity in Copper-Based Catalysts. *J. Am. Chem. Soc.* **2007**, *129*, 3490–3491. [CrossRef]
36. Kwong, F.Y.; Buchwald, S.L. Mild and Efficient Copper-Catalyzed Amination of Aryl Bromides with Primary Alkylamines. *Org. Lett.* **2003**, *5*, 793–796. [CrossRef]
37. Bernhardson, D.J.; Widlicka, D.W.; Singer, R.A. Cu-Catalyzed Couplings of Heteroaryl Primary Amines and (Hetero)aryl Bromides with 6-Hydroxypicolinamide Ligands. *Org. Proc. Res. Dev.* **2019**, *23*, 1538–1551. [CrossRef]
38. Modak, A.; Nett, A.J.; Swift, E.C.; Haibach, M.C.; Chan, V.S.; Franczyk, T.S.; Shekhar, S.; Cook, S.P. Cu-Catalyzed C–N Coupling with Sterically Hindered Partners. *ACS Catal.* **2020**, *10*, 10495–10499. [CrossRef]
39. Kim, S.-T.; Strauss, M.J.; Cabré, A.; Buchwald, S.L. Room-Temperature Cu-Catalyzed Amination of Aryl Bromides Enabled by DFT-Guided Ligand Design. *J. Am. Chem. Soc.* **2023**, *145*, 6966–6975. [CrossRef]
40. Zhou, W.; Fan, M.; Yin, J.; Jiang, Y.; Ma, D. CuI/Oxalic Diamide Catalyzed Coupling Reaction of (Hetero)Aryl Chlorides and Amines. *J. Am. Chem. Soc.* **2015**, *137*, 11942–11945. [CrossRef]
41. Chen, Z.; Ma, D. Cu/N,N′-Dibenzyloxalamide-Catalyzed *N*-Arylation of Heteroanilines. *Org. Lett.* **2019**, *21*, 6874–6878. [CrossRef] [PubMed]
42. Li, S.; Huang, X.; Gao, Y.; Jin, J. Oxalamide/Amide Ligands: Enhanced and Copper-Catalyzed C–N Cross-Coupling for Triarylamine Synthesis. *Org. Lett.* **2022**, *24*, 5817–5824. [CrossRef] [PubMed]
43. Ma, D.; Cai, Q. Copper/Amino Acid Catalyzed Cross-Couplings of Aryl and Vinyl Halides with Nucleophiles. *Acc. Chem. Res.* **2008**, *41*, 1450–1460. [CrossRef] [PubMed]
44. Beletskaya, I.P.; Cheprakov, A.V. The Complementary Competitors: Palladium and Copper in C–N Cross-Coupling Reactions. *Organometallics* **2012**, *31*, 7753–7808. [CrossRef]
45. Senra, J.D.; Aguiar, L.C.S.; Simas, A.B.C. Recent Progress in Transition-Metal-Catalyzed C-N Cross-Couplings: Emerging Approaches Towards Sustainability. *Curr. Org. Synth.* **2011**, *8*, 53–78. [CrossRef]
46. Sambiagio, C.; Marsden, S.P.; Blacker, A.J.; McGowan, P.C. Copper catalysed Ullmann type chemistry: From mechanistic aspects to modern development. *Chem. Soc. Rev.* **2014**, *43*, 3525–3550. [CrossRef] [PubMed]
47. Evano, G.; Blanchard, N.; Toumi, M. Copper-Mediated Coupling Reactions and Their Applications in Natural Products and Designed Biomolecules Synthesis. *Chem. Rev.* **2008**, *108*, 3054–3131. [CrossRef]
48. Okano, K.; Tokuyama, H.; Fukuyama, T. Copper-mediated aromatic amination reaction and its application to the total synthesis of natural products. *Chem. Commun.* **2014**, *50*, 13650–13663. [CrossRef]
49. Lee, J.; Panek, J.S. Application of Copper-Mediated C–N Bond Formation in Complex Molecules Synthesis. In *Copper-Mediated Cross-Coupling Reactions*; John Wiley & Sons Inc.: Hoboken, NJ, USA, 2013; pp. 589–641. [CrossRef]
50. Junge, K.; Wienhöfer, G.; Beller, M.; Tlili, A.; Evano, G.; Taillefer, M.; Kempe, R.; Malbertz, C.; Klankermayer, J. New Trends in Organometallic Catalysts. In *Applied Homogeneous Catalysis with Organometallic Compounds: A Comprehensive Handbook in Three Volumes*, 3rd ed.; Cornils, B., Herrmann, W.A., Beller, M., Paciello, R., Eds.; John Wiley & Sons Inc.: Hoboken, NJ, USA, 2017.
51. Shaughnessy, K.H.; Ciganek, E.; De Vasher, R.B.; Denmark, S.E. *Copper-Catalyzed Amination of Aryl and Alkenyl Electrophiles*; John Wiley & Sons Inc.: Hoboken, NJ, USA, 2017.
52. Neetha, M.; Saranya, S.; Ann Harry, N.; Anilkumar, G. Recent Advances and Perspectives in the Copper-Catalysed Amination of Aryl and Heteroaryl Halides. *ChemistrySelect* **2020**, *5*, 736–753. [CrossRef]
53. Weidlich, T.; Špryncová, M.; Čegan, A. Copper-Catalyzed Reactions of Aryl Halides with *N*-Nucleophiles and Their Possible Application for Degradation of Halogenated Aromatic Contaminants. *Catalysts* **2022**, *12*, 911. [CrossRef]
54. Hosseinzadeh, R.; Aghili, N.; Tajbakhsh, M. SBA-15 Immobilized Phenanthroline–Copper(I) Complex as a Recyclable Efficient Catalyst for N-Arylation of Amides and N–H Heterocycles with Aryl Halides. *Catal. Lett.* **2016**, *146*, 193–203. [CrossRef]
55. Niakan, M.; Asadi, Z.; Zare, S. Preparation, Characterization and Application of Copper Schiff base Complex Supported on MCM-41 as a Recyclable Catalyst for the Ullmann-type N-arylation Reaction. *ChemistrySelect* **2020**, *5*, 40–48. [CrossRef]
56. Veisi, H.; Hamelian, M.; Hemmati, S.; Dalvand, A. CuI catalyst heterogenized on melamine-pyridines immobilized SBA-15: Heterogeneous and recyclable nanocatalyst for Ullmann-type CN coupling reactions. *Tetrahedron Lett.* **2017**, *58*, 4440–4446. [CrossRef]
57. Hemmati, S.; Ahany Kamangar, S.; Yousefi, M.; Hashemi Salehi, M.; Hekmati, M. Cu(I)-anchored polyvinyl alcohol coated-magnetic nanoparticles as heterogeneous nanocatalyst in Ullmann-type C–N coupling reactions. *Appl. Organomet. Chem.* **2020**, *34*, e5611. [CrossRef]
58. Islam, M.; Mondal, S.; Mondal, P.; Roy, A.S.; Tuhina, K.; Mobarok, M.; Paul, S.; Salam, N.; Hossain, D. An Efficient Recyclable Polymer Supported Copper(II) Catalyst for C–N Bond Formation by N-Arylation. *Catal. Lett.* **2011**, *141*, 1171–1181. [CrossRef]
59. Arundhathi, R.; Kumar, D.C.; Sreedhar, B. C–N Bond Formation Catalysed by CuI Bonded to Polyaniline Nanofiber. *Eur. J. Org. Chem.* **2010**, *2010*, 3621–3630. [CrossRef]
60. Islam, S.M.; Salam, N.; Mondal, P.; Roy, A.S.; Ghosh, K.; Tuhina, K. A highly active reusable polymer anchored copper catalyst for C-O, C-N and C-S cross coupling reactions. *J. Mol. Catal. A Chem.* **2014**, *387*, 7–19. [CrossRef]
61. Esmaeilpour, M.; Sardarian, A.R.; Firouzabadi, H. Dendrimer-encapsulated Cu(II) nanoparticles immobilized on superparamagnetic Fe_3O_4@SiO_2 nanoparticles as a novel recyclable catalyst for N-arylation of nitrogen heterocycles and green synthesis of 5-substituted 1H-tetrazoles. *Appl. Organomet. Chem.* **2018**, *32*, e4300. [CrossRef]

62. Chouhan, G.; Wang, D.; Alper, H. Magnetic nanoparticle-supported proline as a recyclable and recoverable ligand for the CuI catalyzed arylation of nitrogen nucleophiles. *Chem. Commun.* **2007**, *45*, 4809–4811. [CrossRef]
63. Zahmatkesh, S.; Esmaeilpour, M.; Javidi, J. 1,4-Dihydroxyanthraquinone–copper(ii) supported on superparamagnetic Fe_3O_4@SiO_2: An efficient catalyst for N-arylation of nitrogen heterocycles and alkylamines with aryl halides and click synthesis of 1-aryl-1,2,3-triazole derivatives. *RSC Adv.* **2016**, *6*, 90154–90164. [CrossRef]
64. Sardarian, A.R.; Eslahi, H.; Esmaeilpour, M. Copper(II) Complex Supported on Fe_3O_4@SiO_2 Coated by Polyvinyl Alcohol as Reusable Nanocatalyst in N-Arylation of Amines and N(H)- Heterocycles and Green Synthesis of 1H-Tetrazoles. *ChemistrySelect* **2018**, *3*, 1499–1511. [CrossRef]
65. Paine, A.J. Mechanisms and models for copper mediated nucleophilic aromatic substitution. 2. Single catalytic species from three different oxidation states of copper in an Ullmann synthesis of triarylamines. *J. Am. Chem. Soc.* **1987**, *109*, 1496–1502. [CrossRef]
66. Aalten, H.L.; van Koten, G.; Grove, D.M.; Kuilman, T.; Piekstra, O.G.; Hulshof, L.A.; Sheldon, R.A. The copper catalysed reaction of sodium methoxide with aryl bromides. A mechanistic study leading to a facile synthesis of anisole derivatives. *Tetrahedron* **1989**, *45*, 5565–5578. [CrossRef]
67. Komori, T.; Satoh, N.; Yokoshima, S.; Fukuyama, T. Copper-Mediated Aryl Amination: In Situ Generation of an Active Copper(I) Species. *Synlett* **2011**, *2011*, 1859–1862. [CrossRef]
68. Meng, F.; Zhu, X.; Li, Y.; Xie, J.; Wang, B.; Yao, J.; Wan, Y. Efficient Copper-Catalyzed Direct Amination of Aryl Halides Using Aqueous Ammonia in Water. *Eur. J. Org. Chem.* **2010**, *2010*, 6149–6152. [CrossRef]
69. Quan, Z.; Xia, H.; Zhang, Z.; Da, Y.; Wang, X. Copper-Catalyzed Amination of Aryl Halides with Aqueous Ammonia under Mild Conditions. *Chin. J. Chem.* **2013**, *31*, 501–506. [CrossRef]
70. Fantasia, S.; Windisch, J.; Scalone, M. Ligandless Copper-Catalyzed Coupling of Heteroaryl Bromides with Gaseous Ammonia. *Adv. Synth. Catal.* **2013**, *355*, 627–631. [CrossRef]
71. Shang, Z.; Yang, L.; Chang, G. Synthesis of high-performance polymers via copper-catalyzed amination of dibromoarenes with primary aromatic ether diamines. *Macromol. Res.* **2015**, *23*, 937–943. [CrossRef]
72. Jiao, J.; Zhang, X.-R.; Chang, N.-H.; Wang, J.; Wei, J.-F.; Shi, X.-Y.; Chen, Z.-G. A Facile and Practical Copper Powder-Catalyzed, Organic Solvent- and Ligand-Free Ullmann Amination of Aryl Halides. *J. Org. Chem.* **2011**, *76*, 1180–1183. [CrossRef]
73. Sperotto, E.; van Klink, G.P.M.; van Koten, G.; de Vries, J.G. The mechanism of the modified Ullmann reaction. *Dalton Trans.* **2010**, *39*, 10338–10351. [CrossRef]
74. Mansour, M.; Giacovazzi, R.; Ouali, A.; Taillefer, M.; Jutand, A. Activation of aryl halides by Cu0/1,10-phenanthroline: Cu0 as precursor of CuI catalyst in cross-coupling reactions. *Chem. Commun.* **2008**, *45*, 6051–6053. [CrossRef] [PubMed]
75. Guo, Z.; Guo, J.; Song, Y.; Wang, L.; Zou, G. Hemilabile-coordinated copper promoted amination of aryl halides with ammonia in aqueous ethylene glycol under atmosphere pressure. *Appl. Organomet. Chem.* **2009**, *23*, 150–153. [CrossRef]
76. Lefèvre, G.; Franc, G.; Adamo, C.; Jutand, A.; Ciofini, I. Influence of the Formation of the Halogen Bond ArX—N on the Mechanism of Diketonate Ligated Copper-Catalyzed Amination of Aromatic Halides. *Organometallics* **2012**, *31*, 914–920. [CrossRef]
77. Xiang, S.-K.; Zhang, D.-X.; Hu, H.; Shi, J.-L.; Liao, L.-G.; Feng, C.; Wang, B.-Q.; Zhao, K.-Q.; Hu, P.; Yang, H.; et al. Synthesis of N-Arylamides by Copper-Catalyzed Amination of Aryl Halides with Nitriles. *Adv. Synth. Catal.* **2013**, *355*, 1495–1499. [CrossRef]
78. Huffman, L.M.; Stahl, S.S. Carbon–Nitrogen Bond Formation Involving Well-Defined Aryl–Copper(III) Complexes. *J. Am. Chem. Soc.* **2008**, *130*, 9196–9197. [CrossRef] [PubMed]
79. Casitas, A.; King, A.E.; Parella, T.; Costas, M.; Stahl, S.S.; Ribas, X. Direct observation of CuI/CuIII redox steps relevant to Ullmann-type coupling reactions. *Chem. Sci.* **2010**, *1*, 326–330. [CrossRef]
80. Casitas, A.; Ribas, X. The role of organometallic copper(III) complexes in homogeneous catalysis. *Chem. Sci.* **2013**, *4*, 2301–2318. [CrossRef]
81. Bacon, R.G.R.; Karim, A. Metal ions and complexes in organic reactions. Part XV. Copper-catalysed substitutions of aryl halides by phthalimide ion. *J. Chem. Soc. Perkin Trans.* **1973**, 272–278. [CrossRef]
82. Wanka, L.; Iqbal, K.; Schreiner, P.R. The Lipophilic Bullet Hits the Targets: Medicinal Chemistry of Adamantane Derivatives. *Chem. Rev.* **2013**, *113*, 3516–3604. [CrossRef]
83. Sonkusare, S.K.; Kaul, C.L.; Ramarao, P. Dementia of Alzheimer's disease and other neurodegenerative disorders—Memantine, a new hope. *Pharmacol. Res.* **2005**, *51*, 1–17. [CrossRef]
84. Grekhova, T.V.; Gainetdinov, R.R.; Sotnikova, T.D.; Krasnykh, L.M.; Kudrin, V.S.; Sergeeva, S.A.; Morozov, I.S. Effect of bromantane, a new immunostimulating agent with psychostimulating activity, on the release and metabolism of dopamine in the striatum of freely moving rats. A microdialysis study. *Bull. Exp. Biol. Med.* **1995**, *119*, 294–296. [CrossRef]
85. Morozov, I.S.; Klimova, N.V.; Lavrova, L.N.; Avdyunina, N.I.; Pyatin, B.M.; Troitskaya, V.S.; Bykov, N.P. N-adamantyl derivatives of aromatic amines. Part I. Synthesis and neurotropic activity of N-(adamant-2-yl)anilines. *Pharm. Chem. J.* **1998**, *32*, 1–4. [CrossRef]
86. Panchenko, S.P.; Abel, A.S.; Averin, A.D.; Maloshitskaya, O.A.; Savelyev, E.N.; Orlinson, B.S.; Novakov, I.A.; Beletskaya, I.P. Arylation of adamantanamines: VIII. Optimization of the catalytic system for copper-catalyzed arylation of adamantane-containing amines. *Russ. J. Org. Chem.* **2017**, *53*, 1497–1504. [CrossRef]
87. Averin, A.D.; Panchenko, S.P.; Abel, A.S.; Maloshitskaya, O.A.; Butov, G.M.; Savelyev, E.N.; Orlinson, B.S.; Novakov, I.A.; Beletskaya, I.P. Arylation of adamantanamines: IX. Copper(I)-catalyzed arylation of adamantane-containing amines. *Russ. J. Org. Chem.* **2017**, *53*, 1788–1798. [CrossRef]

88. Panchenko, S.P.; Abel, A.C.; Averin, A.D.; Maloshitskaya, O.A.; Savelyev, E.N.; Orlinson, B.S.; Novakov, I.A.; Beletskaya, I.P. CuI-catalyzed N,N′-diarylation of diamines of adamantane series. *Russ. Chem. Bull.* **2016**, *65*, 1550–1555. [CrossRef]
89. Murashkina, A.V.; Averin, A.D.; Panchenko, S.P.; Abel, A.S.; Maloshitskaya, O.A.; Savelyev, E.N.; Orlinson, B.S.; Novakov, I.A.; Correia, C.R.D.; Beletskaya, I.P. Comparison of the Catalytic Activities of Copper(I) Iodide and Copper Nanoparticles in the N-Arylation of Adamantane-Containing Amines. *Russ. J. Org. Chem.* **2022**, *58*, 15–24. [CrossRef]
90. Kivitz, A.J.; Gutierrez-Ureña, S.R.; Poiley, J.; Genovese, M.C.; Kristy, R.; Shay, K.; Wang, X.; Garg, J.P.; Zubrzycka-Sienkiewicz, A. Peficitinib, a JAK Inhibitor, in the Treatment of Moderate-to-Severe Rheumatoid Arthritis in Patients With an Inadequate Response to Methotrexate. *Arthritis Rheumatol.* **2017**, *69*, 709–719. [CrossRef]
91. Leovac, V.M.; Rodić, M.V.; Jovanović, L.S.; Joksović, M.D.; Stanojković, T.; Vujčić, M.; Sladić, D.; Marković, V.; Vojinović-Ješić, L.S. Transition Metal Complexes with 1-Adamantoyl Hydrazones—Cytotoxic Copper(II) Complexes of Tri- and Tetradentate Pyridine Chelators Containing an Adamantane Ring System. *Eur. J. Inorg. Chem.* **2015**, *2015*, 882–895. [CrossRef]
92. Ryu, J.H.; Kim, S.; Han, H.Y.; Son, H.J.; Lee, H.J.; Shin, Y.A.; Kim, J.-S.; Park, H.-g. Synthesis and biological evaluation of picolinamides as potent inhibitors of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1). *Bioorg. Med. Chem. Lett.* **2015**, *25*, 695–700. [CrossRef]
93. Rohde, J.J.; Pliushchev, M.A.; Sorensen, B.K.; Wodka, D.; Shuai, Q.; Wang, J.; Fung, S.; Monzon, K.M.; Chiou, W.J.; Pan, L.; et al. Discovery and Metabolic Stabilization of Potent and Selective 2-Amino-N-(adamant-2-yl) Acetamide 11β-Hydroxysteroid Dehydrogenase Type 1 Inhibitors. *J. Med. Chem.* **2007**, *50*, 149–164. [CrossRef]
94. Sorensen, B.; Rohde, J.; Wang, J.; Fung, S.; Monzon, K.; Chiou, W.; Pan, L.; Deng, X.; Stolarik, D.; Frevert, E.U.; et al. Adamantane 11-β-HSD-1 inhibitors: Application of an isocyanide multicomponent reaction. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5958–5962. [CrossRef] [PubMed]
95. Liu, S.; Qian, P.; Wan, F.-X.; Shi, Y.-H.; Jiang, L. Design, synthesis, and biological activity of novel 2-(pyridin-3-yl)ethan-1-one oxime ethers bearing adamantane moiety. *J. Chin. Chem. Soc.* **2019**, *66*, 330–334. [CrossRef]
96. Collins, K.C.; Janda, K.D. Investigating Hapten Clustering as a Strategy to Enhance Vaccines against Drugs of Abuse. *Bioconjug. Chem.* **2014**, *25*, 593–600. [CrossRef] [PubMed]
97. Weigel, W.K., III; Dang, H.T.; Feceub, A.; Martin, D.B.C. Direct radical functionalization methods to access substituted adamantanes and diamondoids. *Org. Biomol. Chem.* **2022**, *20*, 10–36. [CrossRef]
98. Zhou, L.; Togo, H. Introduction of Heteroaromatic Bases onto Cycloalkanes with BPO. *Eur. J. Org. Chem.* **2019**, *2019*, 1627–1634. [CrossRef]
99. Zhao, H.; Li, Z.; Jin, J. Green oxidant H_2O_2 as a hydrogen atom transfer reagent for visible light-mediated Minisci reaction. *New J. Chem.* **2019**, *43*, 12533–12537. [CrossRef]
100. Perry, I.B.; Brewer, T.F.; Sarver, P.J.; Schultz, D.M.; DiRocco, D.A.; MacMillan, D.W.C. Direct arylation of strong aliphatic C–H bonds. *Nature* **2018**, *560*, 70–75. [CrossRef]
101. Abel, A.S.; Averin, A.D.; Anokhin, M.V.; Maloshitskaya, O.A.; Butov, G.M.; Savelyev, E.N.; Orlinson, B.S.; Novakov, I.A.; Beletskaya, I.P. Arylation of adamantanamines: VII. Copper(I)-catalyzed N-heteroarylation of adamantane-containing amines with halopyridines. *Russ. J. Org. Chem.* **2015**, *51*, 301–308. [CrossRef]
102. Abel, A.S.; Kotovshchikov, Y.N.; Averin, A.D.; Maloshitskaya, O.A.; Savelyev, E.N.; Orlinson, B.S.; Novakov, I.A.; Beletskaya, I.P. Problem of Regioselectivity in the Amination of 2-Fluoro-5-iodopyridine with Adamantylalkyl Amines. *Heterocycles* **2019**, *99*, 1342–1354. [CrossRef]
103. Scherman, M.S.; North, E.J.; Jones, V.; Hess, T.N.; Grzegorzewicz, A.E.; Kasagami, T.; Kim, I.-H.; Merzlikin, O.; Lenaerts, A.J.; Lee, R.E.; et al. Screening a library of 1600 adamantyl ureas for anti-Mycobacterium tuberculosis activity in vitro and for better physical chemical properties for bioavailability. *Bioorg. Med. Chem.* **2012**, *20*, 3255–3262. [CrossRef]
104. Al-Omar, M.A.; Al-Abdullah, E.S.; Shehata, I.A.; Habib, E.E.; Ibrahim, T.M.; El-Emam, A.A. Synthesis, Antimicrobial, and Anti-inflammatory Activities of Novel 5-(1-Adamantyl)-4-arylideneamino-3-mercapto-1,2,4-triazoles and Related Derivatives. *Molecules* **2010**, *15*, 2526–2550. [CrossRef] [PubMed]
105. Yu, X.; Zhang, M.; Annamalai, T.; Bansod, P.; Narula, G.; Tse-Dinh, Y.-C.; Sun, D. Synthesis, evaluation, and CoMFA study of fluoroquinophenoxazine derivatives as bacterial topoisomerase IA inhibitors. *Eur. J. Med. Chem.* **2017**, *125*, 515–527. [CrossRef] [PubMed]
106. O'Brien-Brown, J.; Jackson, A.; Reekie, T.A.; Barron, M.L.; Werry, E.L.; Schiavini, P.; McDonnell, M.; Munoz, L.; Wilkinson, S.; Noll, B.; et al. Discovery and pharmacological evaluation of a novel series of adamantyl cyanoguanidines as P2X7 receptor antagonists. *Eur. J. Med. Chem.* **2017**, *130*, 433–439. [CrossRef] [PubMed]
107. Udagawa, S.; Sakami, S.; Takemura, T.; Sato, M.; Arai, T.; Nitta, A.; Aoki, T.; Kawai, K.; Iwamura, T.; Okazaki, S.; et al. Discovery of novel 7-membered cyclic amide derivatives that inhibit 11beta-hydroxysteroid dehydrogenase type 1. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 1617–1621. [CrossRef] [PubMed]
108. Berglund, S.; Egner, B.J.; Gradén, H.; Gradén, J.; Morgan, D.G.A.; Inghardt, T.; Giordanetto, F. Optimization of piperidin-4-yl-urea-containing melanin-concentrating hormone receptor 1 (MCH-R1) antagonists: Reducing hERG-associated liabilities. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4274–4279. [CrossRef]
109. Brogi, S.; Corelli, F.; Di Marzo, V.; Ligresti, A.; Mugnaini, C.; Pasquini, S.; Tafi, A. Three-dimensional quantitative structure–selectivity relationships analysis guided rational design of a highly selective ligand for the cannabinoid receptor 2. *Eur. J. Med. Chem.* **2011**, *46*, 547–555. [CrossRef]

110. Lyakhovich, M.S.; Murashkina, A.V.; Averin, A.D.; Abel, A.S.; Maloshitskaya, O.A.; Savelyev, E.N.; Orlinson, B.S.; Beletskaya, I.P. Arylation of Adamantanamines: X. Palladium- and Copper-Catalyzed Heteroarylation of Adamantane-Containing Amines with Bromopyridines. *Russ. J. Org. Chem.* **2019**, *55*, 737–747. [CrossRef]
111. Lyakhovich, M.S.; Murashkina, A.V.; Panchenko, S.P.; Averin, A.D.; Abel, A.S.; Maloshitskaya, O.A.; Savelyev, E.N.; Orlinson, B.S.; Novakov, I.A.; Beletskaya, I.P. Arylation of Adamantanamines: XI. Comparison of the Catalytic Efficiency of Palladium and Copper Complexes in Reactions of Adamantanamines with Fluorinated 2-Bromopyridines. *Russ. J. Org. Chem.* **2021**, *57*, 768–783. [CrossRef]
112. Hajipour, A.R.; Dordahan, F.; Rafiee, F.; Mahdavi, M. C–N cross-coupling reaction catalysed by efficient and reusable CuO/SiO_2 nanoparticles under ligand-free conditions. *Appl. Organomet. Chem.* **2014**, *28*, 809–813. [CrossRef]
113. Nador, F.; Volpe, M.A.; Alonso, F.; Radivoy, G. Synthesis of N-aryl imidazoles catalyzed by copper nanoparticles on nanosized silica-coated maghemite. *Tetrahedron* **2014**, *70*, 6082–6087. [CrossRef]
114. Mitrofanov, A.Y.; Murashkina, A.V.; Martín-García, I.; Alonso, F.; Beletskaya, I.P. Formation of C–C, C–S and C–N bonds catalysed by supported copper nanoparticles. *Catal. Sci. Technol.* **2017**, *7*, 4401–4412. [CrossRef]
115. Mondal, P.; Sinha, A.; Salam, N.; Roy, A.S.; Jana, N.R.; Islam, S.M. Enhanced catalytic performance by copper nanoparticle–graphene based composite. *RSC Adv.* **2013**, *3*, 5615–5623. [CrossRef]
116. Gopiraman, M.; Ganesh Babu, S.; Khatri, Z.; Kai, W.; Kim, Y.A.; Endo, M.; Karvembu, R.; Kim, I.S. An efficient, reusable copper-oxide/carbon-nanotube catalyst for N-arylation of imidazole. *Carbon* **2013**, *62*, 135–148. [CrossRef]
117. Khalil, A.; Jouiad, M.; Khraisheh, M.; Hashaikeh, R. Facile Synthesis of Copper Oxide Nanoparticles via Electrospinning. *J. Nanomater.* **2014**, *2014*, 438407. [CrossRef]
118. Jammi, S.; Sakthivel, S.; Rout, L.; Mukherjee, T.; Mandal, S.; Mitra, R.; Saha, P.; Punniyamurthy, T. CuO Nanoparticles Catalyzed C–N, C–O, and C–S Cross-Coupling Reactions: Scope and Mechanism. *J. Org. Chem.* **2009**, *74*, 1971–1976. [CrossRef]
119. Suramwar, N.V.; Thakare, S.R.; Karade, N.N.; Khaty, N.T. Green synthesis of predominant (111) facet CuO nanoparticles: Heterogeneous and recyclable catalyst for N-arylation of indoles. *J. Mol. Catal. A Chem.* **2012**, *359*, 28–34. [CrossRef]
120. Rout, L.; Jammi, S.; Punniyamurthy, T. Novel CuO Nanoparticle Catalyzed C–N Cross Coupling of Amines with Iodobenzene. *Org. Lett.* **2007**, *9*, 3397–3399. [CrossRef]
121. Reddy, K.H.V.; Satish, G.; Ramesh, K.; Karnakar, K.; Nageswar, Y.V.D. An efficient synthesis of N-substituted indoles from indoline/indoline carboxylic acid via aromatization followed by C–N cross-coupling reaction by using nano copper oxide as a recyclable catalyst. *Tetrahedron Lett.* **2012**, *53*, 3061–3065. [CrossRef]
122. Murashkina, A.V.; Kuliukhina, D.S.; Averin, A.D.; Abel, A.S.; Savelyev, E.N.; Orlinson, B.S.; Novakov, I.A.; Correia, C.R.D.; Beletskaya, I.P. A comparison of homogeneous and heterogeneous copper catalyzed arylation of amines. *Mendeleev Commun.* **2022**, *32*, 91–93. [CrossRef]
123. Fomenko, V.I.; Murashkina, A.V.; Averin, A.D.; Shesterkina, A.A.; Beletskaya, I.P. Unsupported Copper Nanoparticles in the Arylation of Amines. *Catalysts* **2023**, *13*, 331. [CrossRef]
124. Kuliukhina, D.S.; Averin, A.D.; Panchenko, S.P.; Abel, A.S.; Savelyev, E.N.; Orlinson, B.S.; Novakov, I.A.; Correia, C.R.D.; Beletskaya, I.P. CuI and Copper Nanoparticles in the Catalytic Amination of 2-Halopyridines. *Russ. J. Org. Chem.* **2022**, *58*, 167–174. [CrossRef]
125. Pegg, A.E.; Casero, R.A. Current Status of the Polyamine Research Field. In *Polyamines: Methods and Protocols*; Pegg, A., Casero, R., Jr., Eds.; Humana Press: Totowa, NJ, USA, 2011; Volume 720, pp. 3–35. [CrossRef]
126. Díaz, J.E.; Bisceglia, J.Á.; Mollo, M.C.; Orelli, L.R. 1,n-Diamines. Part 2: Synthesis of acyclic and heterocyclic N-arylputrescine derivatives. *Tetrahedron Lett.* **2011**, *52*, 1895–1897. [CrossRef]
127. Bisceglia, J.Á.; García, M.B.; Massa, R.; Magri, M.L.; Zani, M.; Gutkind, G.O.; Orelli, L.R. Synthesis, characterization and biological activity of bis(3-Aryl-1-hexahydropyrimidinyl)methanes. Novel heterocyclic polyamine derivatives. *J. Heterocycl. Chem.* **2004**, *41*, 85–90. [CrossRef]
128. Haffner, C.D.; Thomson, S.A.; Guo, Y.; Petrov, K.; Larkin, A.; Banker, P.; Schaaf, G.; Dickerson, S.; Gobel, J.; Gillie, D.; et al. Substituted N-{3-[(1,1-dioxido-1,2-benzothiazol-3-yl)(phenyl)amino]propyl}benzamide analogs as potent Kv1.3 ion channel blockers. Part 2. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6989–6992. [CrossRef] [PubMed]
129. Burns, M.R.; LaTurner, S.; Ziemer, J.; McVean, M.; Devens, B.; Carlson, C.L.; Graminski, G.F.; Vanderwerf, S.M.; Weeks, R.S.; Carreon, J. Induction of apoptosis by aryl-substituted diamines: Role of aromatic group substituents and distance between nitrogens. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1263–1267. [CrossRef] [PubMed]
130. Bergeron, R.J.; Weimar, W.R.; Wu, Q.; Feng, Y.; McManis, J.S. Polyamine Analogue Regulation of NMDA MK-801 Binding: A Structure–Activity Study. *J. Med. Chem.* **1996**, *39*, 5257–5266. [CrossRef] [PubMed]
131. da Costa, C.F.; Coimbra, E.S.; Braga, F.G.; dos Reis, R.C.N.; da Silva, A.D.; de Almeida, M.V. Preparation and antileishmanial activity of lipophilic N-alkyl diamines. *Biomed. Pharmacother.* **2009**, *63*, 40–42. [CrossRef] [PubMed]
132. Panchenko, S.P.; Averin, A.D.; Anokhin, M.V.; Maloshitskaya, O.A.; Beletskaya, I.P. Cu(I)-catalyzed N,N′-diarylation of natural diamines and polyamines with aryl iodides. *Beilstein J. Org. Chem.* **2015**, *11*, 2297–2305. [CrossRef]
133. Anokhin, M.V.; Averin, A.D.; Beletskaya, I.P. Copper-Catalyzed Arylation of Oxadiamines and Polyamines. *Eur. J. Org. Chem.* **2011**, *2011*, 6240–6253. [CrossRef]

134. Albert, J.; Bosque, R.; Cadena, M.; D'Andrea, L.; Granell, J.; González, A.; Quirante, J.; Calvis, C.; Messeguer, R.; Badía, J.; et al. A New Family of Doubly Cyclopalladated Diimines. A Remarkable Effect of the Linker between the Metalated Units on Their Cytotoxicity. *Organometallics* **2014**, *33*, 2862–2873. [CrossRef]
135. Li, S.A.; Cadelis, M.M.; Sue, K.; Blanchet, M.; Vidal, N.; Brunel, J.M.; Bourguet-Kondracki, M.-L.; Copp, B.R. 6-Bromoindolglyoxylamido derivatives as antimicrobial agents and antibiotic enhancers. *Bioorg. Med. Chem.* **2019**, *27*, 2090–2099. [CrossRef]
136. Liew, L.P.P.; Pearce, A.N.; Kaiser, M.; Copp, B.R. Synthesis and in vitro and in vivo evaluation of antimalarial polyamines. *Eur. J. Med. Chem.* **2013**, *69*, 22–31. [CrossRef] [PubMed]
137. Devi, J.; Devi, S.; Kumar, A. Synthesis, antibacterial evaluation and QSAR analysis of Schiff base complexes derived from [2,2′-(ethylenedioxy)bis(ethylamine)] and aromatic aldehydes. *MedChemComm* **2016**, *7*, 932–947. [CrossRef]
138. Vennerstrom, J.L.; Ager, A.L.; Dorn, A.; Andersen, S.L.; Gerena, L.; Ridley, R.G.; Milhous, W.K. Bisquinolines. 2. Antimalarial N,N-Bis(7-chloroquinolin-4-yl)heteroalkanediamines. *J. Med. Chem.* **1998**, *41*, 4360–4364. [CrossRef] [PubMed]
139. Chtchigrovsky, M.; Eloy, L.; Jullien, H.; Saker, L.; Ségal-Bendirdjian, E.; Poupon, J.; Bombard, S.; Cresteil, T.; Retailleau, P.; Marinetti, A. Antitumor *trans-N*-Heterocyclic Carbene–Amine–Pt(II) Complexes: Synthesis of Dinuclear Species and Exploratory Investigations of DNA Binding and Cytotoxicity Mechanisms. *J. Med. Chem.* **2013**, *56*, 2074–2086. [CrossRef]
140. Lyakhovich, M.S.; Averin, A.D.; Grigorova, O.K.; Roznyatovsky, V.A.; Maloshitskaya, O.A.; Beletskaya, I.P. Cu(I)- and Pd(0)-Catalyzed Arylation of Oxadiamines with Fluorinated Halogenobenzenes: Comparison of Efficiency. *Molecules* **2020**, *25*, 1084. [CrossRef]
141. Panchenko, S.P.; Averin, A.D.; Lyakhovich, M.S.; Abel, A.S.; Maloshitskaya, O.A.; Beletskaya, I.P. CuI-catalyzed hetarylation of natural di- and polyamines with halopyridines. *Russ. Chem. Bull.* **2017**, *66*, 1611–1617. [CrossRef]
142. Anokhin, M.V.; Averin, A.D.; Panchenko, S.P.; Maloshitskaya, O.A.; Buryak, A.K.; Beletskaya, I.P. Copper(I)-Catalyzed Amination of Halogenopyridines with Polyamines. *Helv. Chim. Acta* **2015**, *98*, 47–59. [CrossRef]
143. Anokhin, M.V.; Averin, A.D.; Panchenko, S.P.; Maloshitskaya, O.A.; Beletskaya, I.P. CuI-mediated modification of polyamines with fluorophore groups. *Mendeleev Commun.* **2015**, *25*, 245–247. [CrossRef]
144. Anokhin, M.V.; Averin, A.D.; Panchenko, S.P.; Maloshitskaya, O.A.; Beletskaya, I.P. Copper(I)-catalyzed amination of halothiophenes with polyamines. *Russ. J. Org. Chem.* **2014**, *50*, 923–927. [CrossRef]
145. Yakushev, A.A.; Averin, A.D.; Anokhin, M.V.; Maloshitskaya, O.A.; Lamaty, F.; Beletskaya, I.P. Copper-catalyzed amination in the synthesis of polyoxadiamine derivatives of aza- and diazacrown ethers. *Macroheterocycles* **2014**, *7*, 358–364. [CrossRef]
146. Yakushev, A.A.; Averin, A.D.; Maloshitskaya, O.A.; Syrbu, S.A.; Koifman, O.I.; Beletskaya, I.P. Palladium- and Copper-Catalyzed Amination of Halogenophenyl Substituted Porphyrins for the Synthesis of Porphyrin-Azacrown Ethers Conjugates and Evaluation of Their Sensing Properties. *Macroheterocycles* **2016**, *9*, 65–72. [CrossRef]
147. West, M.J.; Fyfe, J.W.B.; Vantourout, J.C.; Watson, A.J.B. Mechanistic Development and Recent Applications of the Chan–Lam Amination. *Chem. Rev.* **2019**, *119*, 12491–12523. [CrossRef] [PubMed]
148. Kuliukhina, D.S.; Yakushev, A.A.; Malysheva, A.S.; Averin, A.D.; Beletskaya, I.P. Synthesis of N,N′-Diaryl Diamines and Oxadiamines via Chan–Lam Amination. *Russ. J. Org. Chem.* **2022**, *58*, 1752–1758. [CrossRef]