Copper (I) Catalyzed *N*-Arylation of Azoles, the Recent Developments

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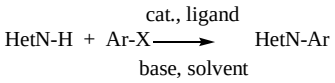
Abstract: *N*-arylated azoles have broad applications either alone or as intermediates in the synthesis of natural products, drugs, polymers, agrochemicals, among other items. Recently, instead of the less universal "classic" methods of arylation, a series of approaches based on the use of a complex of transition metals – derivatives of palladium and copper – was suggested. This mini-review looks into one of the most promising trends in this group of methods, arylation with the use copper(I)-based catalysts. The emphasis is made on a detailed consideration of each arylation method, in order to give the reader a possibility to compare the effectiveness and the limitations of one method or another, evaluate the conditions of conducting a reaction and the availability of reactants. In each subsection, results are presented in chronological order to demonstrate sequential progress in this area.

Keywords: Copper; cross-coupling; *N*-arylation; azoles.

1. INTRODUCTION

N-Arylated heterocycles, especially azoles, are an important class of compounds either as structural motifs in more complex molecules or as molecules themselves; they are found in many natural products, pharmaceutically interesting compounds, and agrochemicals [1]. Until the end of the 20th century, the main synthetic methods for preparation of these compounds were cyclization, involving *N*-arylated precursors [2]; reaction of heterocycles with strong arylation agents, like picrylchloride, in the presence of weak base [3]; and classical copper-catalyzed Ullmann-type coupling, conducted at elevated temperatures in high boiling solvents such as nitrobenzene [4]. However, all of these methods are applicable only to the synthesis of a certain type of compound and are not universal.

The end of the 20th century was marked by the intense introduction of transitional metal catalysts in organic synthesis. For azole *N*-arylation, two types of catalysts were suggested, palladium- and copper-based (Scheme **1**).



Scheme 1.

Despite progress in palladium-catalyzed amination and arylation reactions [5], they did not become popular for *N*-arylation of azoles, mainly due to the high price of catalysts and a preponderance of failed attempts and low yields [6]. In contrast, copper-catalyzed arylation was booming because of its lower cost compared to palladium and its universality.

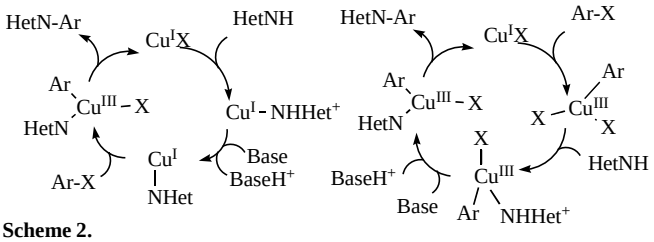
In general, all copper-catalyzed *N*-arylation reactions can be divided into two major groups depending on the type of catalyst. The first group consists of reactions catalyzed by the Cu(II) species; in most cases, these reactions do not require additional ligands and are mainly used to couple azoles to arylboronic acids and related compounds. Today, such arylations have become less popular, mainly because new versatile protocols for coupling azoles with more accessible arylhalogenides have been introduced.

The second group includes reactions catalyzed by Cu(I) compounds, often in the presence of an additional ligand; these reactions are mainly utilized for *N*-arylation by arylhalogenides, and are more flexible, universal, and are thus intensively studied.

In this mini-review, new developments in copper (I) catalyzed arylation of azoles are summarized, starting from the last review on using copper in C-N bond formation in 2004 [7]. In each subsection, results are presented in chronological order to demonstrate sequential progress in this area.

2. Cu (I)-CATALYZED ARYLATION

Unfortunately until now the real mechanism of copper(I) catalyzed transformations still unknown, several attempts was made in this field indicated absence of any radical species on the reaction pathway as suggested for "classic" Ullmann coupling [8]. As believed, copper species is take part in the sequence of oxidative addition, transmetallation, and reductive elimination reactions in analogy with mechanism established experimentally for palladium-catalyzed cross-coupling reactions [5]. Since, in contrast to palladium, for Cu(I) catalyzed transformations no direct experimental evidences available, two equivalent catalytic cycles, including Cu(III) intermediates, was proposed (Scheme **2**) [7].



Scheme 2.

2.1. Cu_2O – Catalyzed Arylation

Copper oxide catalyzed arylation was pioneered by the Cristau group, which found that 5 mol% Cu_2O in the presence of 20 mol% of the chelating ligands Salox (**1**) or Chxn-py-al (**2**) effectively catalyzed arylation of pyrazoles with iodoarenes, bromoarenes, and heteroaryl halides [9].

Scheme **3** shows selected examples of pyrazole arylation; the proposed system demonstrates superior results on a vast number of compounds, producing high yields of products and excellent selectivity. The difficulties arise only with base-sensitive groups such as ethoxycarbonyl; in this case, addition of 3Å molecular sieves is necessary to overcome low yields due to hydrolysis. Also, if *ortho*-substitutents are present, to surmount the difficulties associated with steric hindrance; elevated temperatures, DMF and ligand **2** are required.

This method is also applied to arylation of ring-substituted pyrazoles (Scheme **4**). However, in this case, some problems can arise either with formation of two possible arylated isomers, **3** and **4**, as in case of 3-methylpyrazole, or low reactivity due to steric and electronic effects, as observed for 3,5-dimethylpyrazile.

Recently, the Cristau group has extended the proposed technique to arylation of several other azoles. In case of imidazole; almost the

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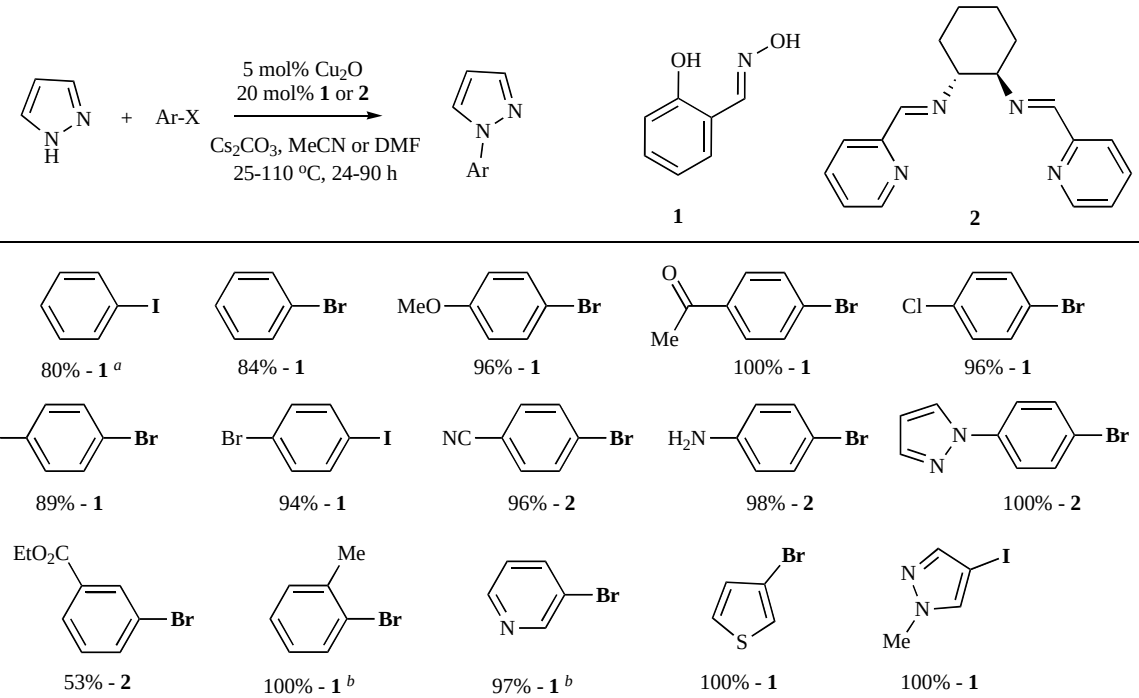
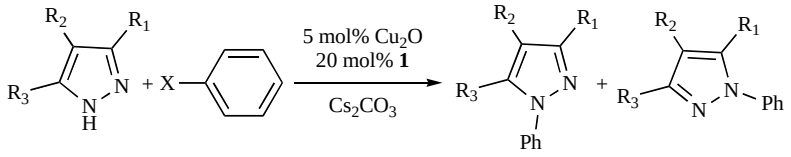


[a] Ligand used indicated by bold number; [b] DMF as solvent

Scheme 3.

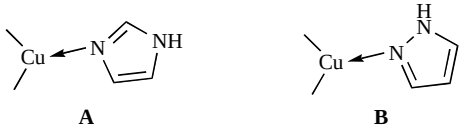


R_1	R_2	R_3	X	Conditions	Yield (%)	3 : 4
CF_3	H	H	I	MeCN (82 °C), 24 h	100	-
CF_3	H	H	Br	MeCN (82 °C), 96 h	81	-
Me	H	H	I	MeCN (82 °C), 24 h	100	4 : 1
Me	H	H	Br	MeCN (82 °C), 96 h	68	3.2 : 1
Me	H	Me	I	MeCN (82 °C), 96 h	12	-
Me	H	Me	I	DMF (110 °C), 24 h	47	-

Scheme 4.

same pattern is observed, and the possibility of one-pot substitution of two halogens in 1,4-diiodobenzene was demonstrated [8]. 1,2,4-Triazole was also regioselectively *N*-arylated at the N1(2) atom by this method, with yields ranging from 79 to 100% depending on conditions [8]. At the same time, 5-phenyltetrazole demonstrated poor nucleophilicity and did not couple even at harsh conditions [8].

Authors propose the following reactivity order for azoles: pyrazole > imidazole > indole ≈ pyrrole > 1,2,4-triazole >> 5-phenyltetrazole, the weaker reactivity of imidazole in contrast to pyrazole they explained by the α-effect of pyrazolate anion, which is responsible to nucleophilicity enhancement and rate-acceleration. This explanation seems to be of low-probability, since in presence of so mild base as Cs_2CO_3 corresponding anions cannot form, one of the possible explanations is formation on initial step of catalytic cycle (Scheme **2**) precoordinated complexes **A** for imidazole and **B** for pyrazole (Scheme **5**), in the last case reaction N-H center is closer to copper and faster reorganized for coupling with haloarenes.



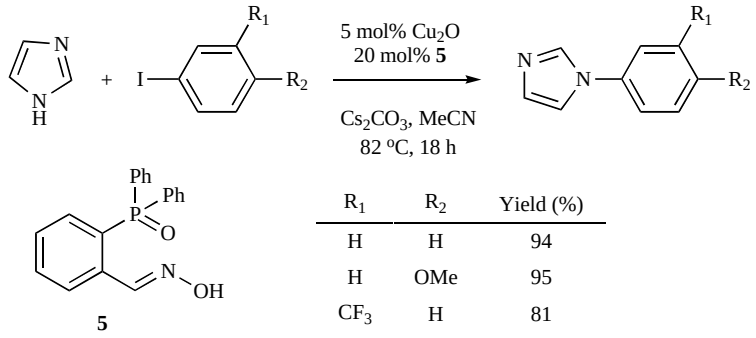
Scheme 5.

In 2005 Wan and his group suggested an easily prepared and highly stable oxime-functionalized phosphine oxide ligand **5** for Cu_2O catalyzed arylation (Scheme **6**) [10].

But a limited number of haloarenes and heterocycles tried did not allow to make any decisions about universality of this method.

4,7-Dimethoxy-1,10-phenantroline (**6**), as was shown by the Buchwald group, can serve as an excellent ligand for *N*-arylation of azoles [11,12]. However, authors used completely different iodo- and bromoarenes in the study and complicated comparisons. Imidazoles were coupled with iodoarenes at only 2.5 mol% Cu_2O and 7.5 mol% ligand loading (Scheme **7**).

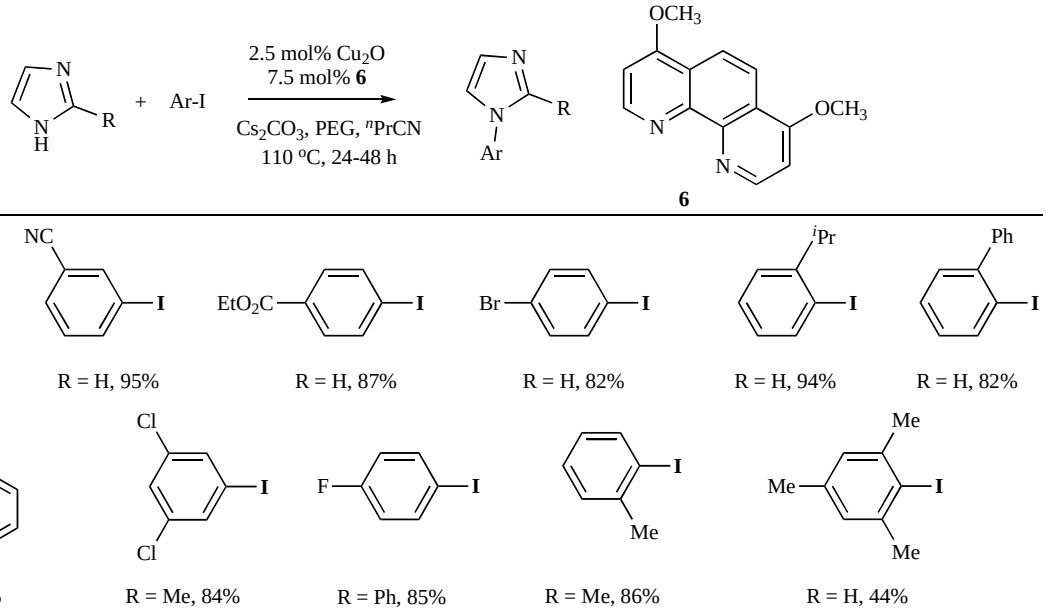
Reactions were conducted in butyronitrile in the presence of PEG as the solid-liquid phase transfer catalyst for Cs_2CO_3. For base-sensitive nitrile and ester groups, lowering the temperature to 80 ℃ was required to obtain good yields. For coupling of hindered sub-



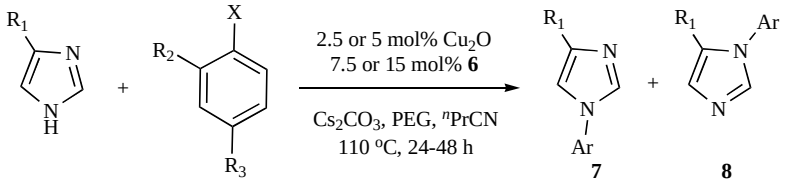
R_1	R_2	Yield (%)
H	H	94
H	OMe	95
CF_3	H	81

5

Scheme 6.



Scheme 7.



X	R_1	R_2	R_3	Yield (%)	**7** : **8**
Br	Ph	H	SMe	96	99 : 1
Br	Me	H	SMe	97	4.4 : 1
I	Me	^{i}Pr	H	82	44 : 1
I	Me	Me	H	91	16 : 1

Scheme 8.

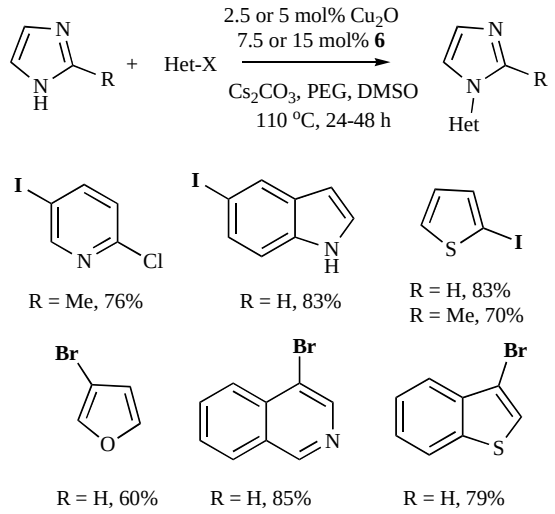
strates, from the other hand, increasing the temperature to 150 ℃ (DMF or NMP) may be needed.

Reaction with arylbromides required higher catalyst loading (5 mol% Cu_2O and 15 mol% **6**) to achieve good yields [11,12]. Thus, pyrazole has been arylated with 4-bromophenol with an 84% yield, for sterically hindered 2-bromotoluene NMP should used as solvent to obtained 85% yield.

Coupling of 4(5)-substituted imidazoles with aryl halides led to a mixture of isomers with preferential formation of the 4-susbtituted one (Scheme **8**) [12].

However, arylation of 4-bromo-2-methylimidazole with 4-iodoanisole gave only a 4-substituted product; as the author has suggested, selectivity was dictated by the increasing steric effects existing in the Cu(III) intermediate (see catalytic cycle on Scheme **2**) when the large bromine-substituents resided at the 5-position relative to the 4-position [12].

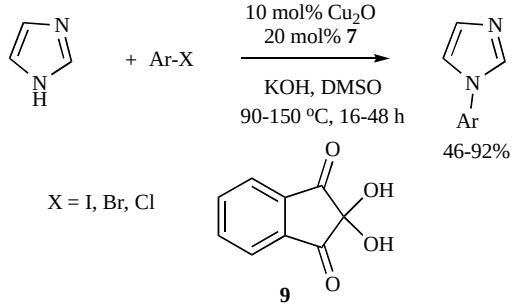
N-heteroarylimidazoles, important substrates for drug discovery, can also be obtained by this method with only exception: instead of butyronitrile, DMSO is needed (Scheme **9**) [12].



Scheme 9.

Besides imidazoles, system Cu_2O/**6** was used for benzimidazole and 2-methylbenzimidazole arylation with aryl bromides [12], but in more drastic conditions, including DMSO and temperatures of 110-130 ℃. Furthermore, for some coupling pairs, instead of Cs_2CO_3/PEG, 7-methyl-1.5.7-triazabicyclo[4.4.0]dec-5-ene (MTBD) has been used as a base due to better yields, as in the reaction of 2-methylbenzimidazole with 3-bromoanisole (82% yield).

Ninhydrin (**9)** can also serve as an effective ligand for *N*-arylation (Scheme **10**) [13].



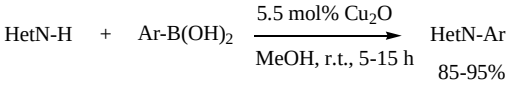
Scheme 10.

The main advantage of this system is simplicity and versatility. The coupling yield is slightly lower than in the above mentioned systems; for example, imidazole interacts with 4-iodoanisole to give 89% yield after 24 h at 110 ℃, but more important is that the method allows reactions to be conducted with chloroarenes. Imidazole with 4-chlorobenzotrifluoride gave product in 90% yield after 24 h at 130 ℃; however, with non- or deactivated arenes, the reaction time and temperature should be increased to achieve satisfactory transformation. Thus, chlorobenzene with imidazole gave only 49% yield of product after 48 h at 150 ℃. Benzimidazole and pyrazole were also tested in the Cu_2O/ninhydrin catalyzed *N*-arylation with iodobenzene and gave 88 and 92% yields, respectively. Unfortunally authors did not discuss the mechanism of the transformation and the question which is not clear, why need so strong base as system KOH/DMSO and which factors let inactive chloroarenes to be involved in arylation?

Although the addition of an organic ligand during the catalysis with Cu_2O seems like a necessity, a series of researches aimed to select the conditions which would allow foregoing their usage, which would lower the costs of conducting a reaction, ease the isolation and cleaning of products. In 2007 Bolm's group found that Cu_2O catalyzed *N*-arylation can be conducted effectively without any ligands [14]. They demonstrated the possibility of conducting the reaction with 10 mol% catalyst loading in the presence of Cs_2CO_3 as base in DMF at 100 or 110 ℃. *N*-arylation of pyrazole has been performed with a broad range of substituted iodo- and bromobenzenes; in the case of iodo- and bromobenzene, yields were 98 and 93%, respectively. Surprisingly, ethyl ester of 4-iodobenzoic acid gave a 99% yield of coupling product, taking into account results of other authors, observed partial hydrolysis of ester group and yield lowering in similar reactions. Benzimidazole and 1,2,4-triazole were arylated by iodobenzene, giving 86% and 76% yields, respectively [14].

The Xu group used stronger base KOH instead of Cs_2CO_3 and no ligand for Cu_2O. They performed imidazole arylation with different iodo- and bromoarenes, as well as with electron deficient chloroarenes, in DMSO at 110-130 ℃ [15]. Reacted with imidazole, 4-iodotoluene gave product in 91% yield, but for ethyl ester of 4-iodobenzoic acid the presence of 4 Å molecular sieves and Cs_2CO_3, to reduce hydrolysis, required to obtain 85% yield. 4-Bromotoluene gave a 88% yield, and 2-chloropyridine 89%. Benzimidazole and pyrazole with iodobenzene gave *N*-arylated products in 88 and 92% yields, respectively. But the more important finding demonstrated, is the possibility of reusing catalyst up to four times without significant loss of activity that is important for further scalability to batch process.

Interesting that not only ligand can be rejected in Cu_2O-catalyzed transformations, but even base, unfortunately, now only in coupling of imidazole, 2-methylimidazole, benzimidazole, and pyrazole with boronic acids as Sreedhar demonstrated (Scheme **11**) [16].



Scheme 11.

In contrast to other methods, this reaction conducted at room temperature, and catalyst can be also reused up to four times. For imidazole, typically 5-6 h was needed, for other azoles, 12-15 h were necessary. Nevertheless, the main disadvantage of boronic acids when compared to aryl halides is a limited assortment and the fact that they are often synthesized from halogen derivatives itself.

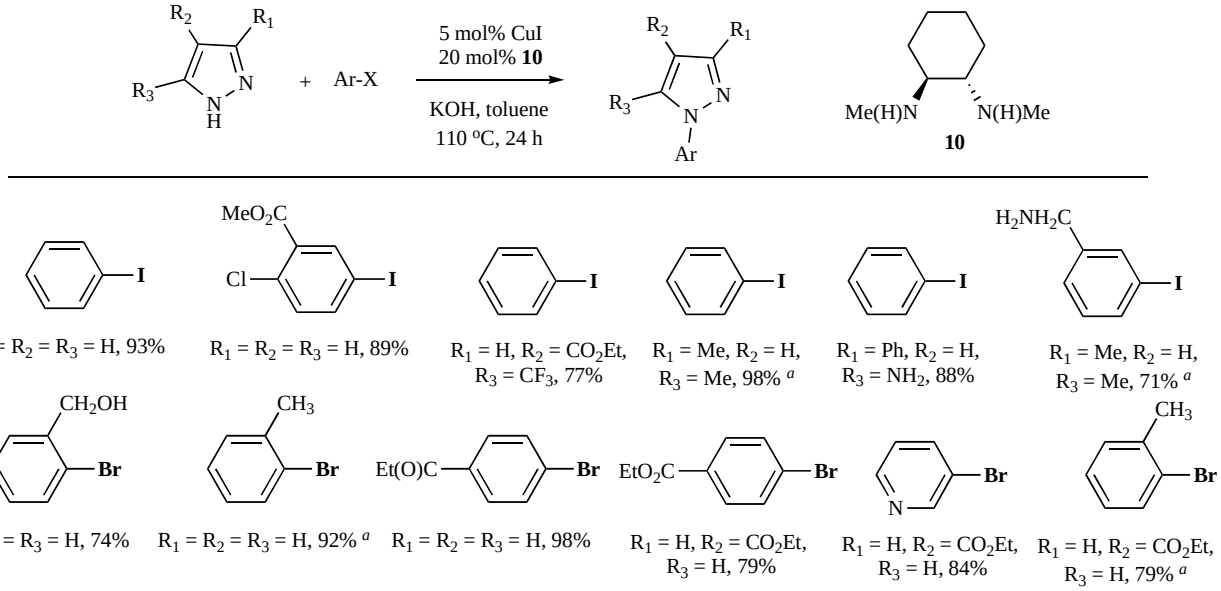
2.2. CuX – Catalyzed Arylation

The idea of using copper (I) salts as catalysts for *N*-arylation was first realized by Buchwald's group, which suggested using $(CuOTf)_2 \cdot PhH$ for coupling of aryl halides with imidazoles in 1999 [17]. Subsequently, each year, several papers have been published on this topic. The most recent achievements in azole *N*-arylation are the following.

Buchwald's group demonstrated the versatility of diamine ligand **10** in CuI-catalyzed arylation of a wide range of pyrazoles (Scheme **12**), indazoles, imidazoles, and triazoles [18].

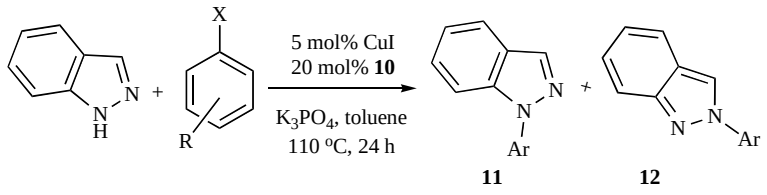
Interesting results have been obtained in the coupling of halobenzenes with indazole. The reaction gave N(1) and N(2) arylated products (Scheme **13**), but the regioselectivity strongly depended on the type of halogen. In the case of aryl bromides, dramatic lowering of regioselectivity has been observed. Authors explain this fact by the low rate of oxidative addition of aryl bromides to the copper catalyst-indazole complex (**13** or **14**). As a result, intermediate **13,** which is a kinetically controlled product, has time to isomerize in some extent into the thermodynamically more stable form **14** [18].

For imidazoles, effective transformation to arylated products was achieved only if Cs_2CO_3 was used as a base and the solvent had been replaced with dioxane or DMF, as example, the 91% yield in reaction of imidazole and benzimidazole with 5-iodo-*meta*-xylene. 4-Methyl- and 4-phenylimidazoles gave coupling products with iodobenzene in 74% and 87% yields, respectively, and only one regioisomer was

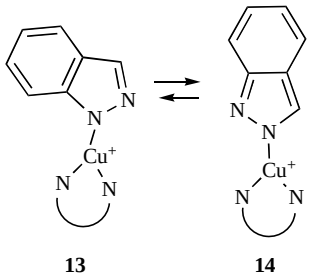


[a] Reaction run neat in aryl halide with no solvent

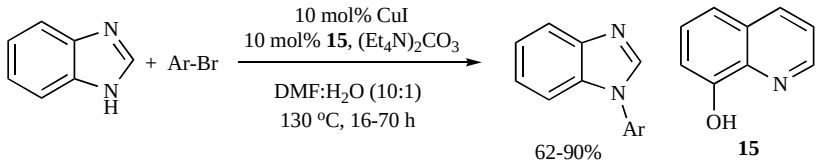
Scheme 12.



X	R	Yield (%)	**11** : **12**
I	4-Me	85	17 : 1
Br	4-Me	75	1.8 : 1
I	3-OMe	92	17 : 1
Br	3-OMe	74	2 : 1
I	2-NH_2	80	20 : 1
Br	2-NH_2	70	1.4 : 1



Scheme 13.



Scheme 14.

formed. Purine can also be phenylated under similar conditions, but the reaction has been conducted at 70 ℃ with 66% yield.

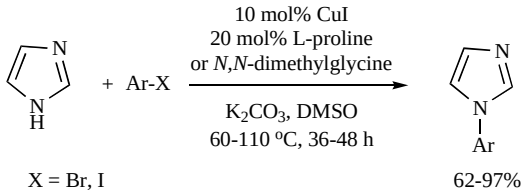
Similarly, triazoles can be arylated by several iodoarenes; thus, *N*-phenyltriazole was obtained with an 89% yield from 1,2,4-triazole and iodobenzene, benzotriazole, under the same conditions, gave a 93% yield of a mixture of N(1) and N(2) isomers with more than 25:1 regioselectivity, and 1,2,3-triazole gave mixture of N(1)/N(2) isomers in which N(1) only slightly predominate [18].

Liu's group has demonstrated the possibility of using 8-hydroxyquinoline (**15**) as a ligand and bis(tetraethylammonium)carbonate (TEAC) as a soluble base for coupling of benzimidazoles with aryl bromides (Scheme **14**) [19].

Although the authors presented their method as very effective and universal, in many cases prolonged reaction times were needed, for *ortho*-substituted aryl bromides, the yields did not exceed 67%, for 2-bromoanisole, partial hydrolysis of the methoxy-group was observed, and for 4-bromobenzonitrile the cyano-group fully converted to amido during the reaction. Also imidazoles have been arylated by this method with different aryl bromides; 80% yield was obtained for coupling with 5-bromo-*meta*-xylene. If *ortho*-substituents were present in the benzene ring or in the 2-position of imidazole, yields dropped to 40-60%.

Readily available and inexpensive amino acids can be excellent ligands for coupling pyrazole, imidazole and benzimidazole with aryl bromides and iodides, as demonstrated by Ma's group (imidazole as an example, Scheme **15**) [20].

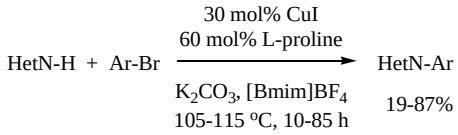
L-Proline is used as a general rule, but if the temperature need to be increased to 110 ℃ for better conversion, *N*,*N*-dimethylglycine is



Scheme 15.

a better choice as ligand in order to avoid self-coupling of L-proline with aryl halides. Not clear the temperature and time selection criteria which authors used, in reaction of 4-bromobenzonitrile with imidazole 85 ℃ and 48 h used whereas for pyrazole 75 ℃ and 45 h, from the other hand with 2-bromopyridine 60 ℃ and 45 h for imidazole, in contrast to 75 ℃ and 48 h for pyrazole used.

Recently, it was shown that CuI/amino acid catalyzed arylation with bromoarenes can be conducted in ionic liquids, becoming very popular as an alternative to classical organic solvents, but in this case, the catalyst and ligand loading should increased to 30 mol% and 60 mol%, respectively (Scheme **16**) [21].



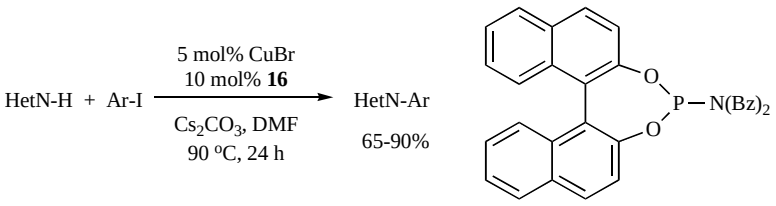
Scheme 16.

As was demonstrated by Li's group, CuBr catalyzed arylation can be conducted in solvent-free conditions if 2-aminopyrimidine-4,6-diol (**17**) is used as ligand and tetra-*n*-butylammonium fluoride (TBAF) as base (Scheme **18**) [23].

Imidazole, 2-methyl, 2-phenylimidazole, benzimidazole, and 2-methylimidazole were investigated. For 2-phenylimidazole yields did not exceed 30%. Mainly electron-deficient bromo-, chloroarenes and heteroarenes have been examined as coupling partners. Interestingly, 4-chloronitrobenzene gave traces of product in reaction with imidazole, whereas with benzimidazole, 74% yield was obtained. Benzimidazole was arylated even with chlorobenzene with a 40% yield, but for other azoles no information is available.

Commercially available pipecolinic acid, studied mainly as a ligand for CuI catalyzed amine arylation [24], was also examined in the reaction of bromobenzene, 4-bromoanisole, and 1-bromo-4-iodobenzene with imidazole, using 10 mol% CuI, 20 mol% of ligand, K_2CO_3 as base at 110 ℃ in DMF; yields of products were 76, 71, and 84%, respectively. In the last case, *N*-(*para*-bromophenyl)imidazole was formed [24].

The main inconvenience of most methods described above is the necessity of using moisture sensitive bases such as Cs_2CO_3, K_2CO_3, and K_3PO_4; as result, some precautions in charging the reaction vessel are needed. Hosseinzadeh and his group suggested a protocol using potassium fluoride supported on alumina (KF/Al_2O_3), a versatile reagent finding applications in a wide range of reactions [25], as a



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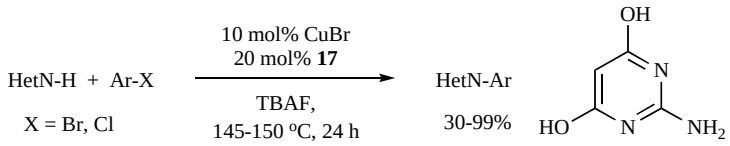
Scheme 17.



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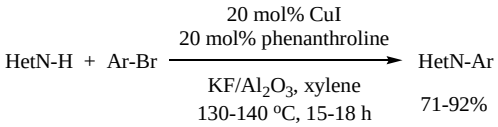
Scheme 18.

1-Butyl-3-methylimidazolium tetrafluoroborate ([Bmim]BF_4) was selected as the reaction media. Coupling of imidazole, 2-methylimidazole, and benzimidazole with different aryl and heteroarylbromides was studied. For example, using 4-bromotoluene and imidazole, the product was obtained with an 82% yield after 24 h. As in other systems, steric hindrances increased the reaction time and lowered yields of product; minimal yields were obtained in the coupling of imidazole with 2-bromo-4-chloro-3-methylbenzothiophene, with only 19% product obtained after 48 h. The main advantage of this system is the possibility of reusing it up to four times as the high polarity of ionic liquid allows it to be extracted with a less polar solvent. As a result, after product extraction and ionic liquid concentration under vacuum, only base and reactant need to be added.

Wan's group did not follow the general trend of using CuI as a catalyst and instead suggested the CuBr/phosphoramidite (**16**) system for imidazole, benzimidazole, and pyrazole *N*-arylation (Scheme **17**) [22].

Among halogenated benzene derivatives as coupling partners, iodoarenes, 2- and 3-bromopyridines were tested. Thus, 4-iodoanisole in reaction with imidazole, benzimidazole, or pyrazole gave corresponding *N*-aryl azoles in 78, 80 and 76% yields, respectively. In the case of electron-deficient iodoarenes, yields were higher, and as for other systems, steric hindrances lowered reaction yields.

base for CuI/phenanthroline catalyzed arylation of azoles with bromoarenes (Scheme **19**) [26].

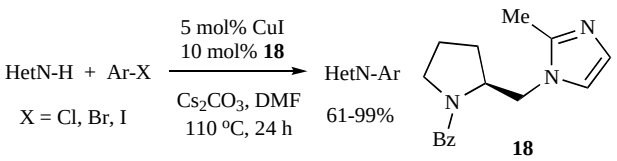


Scheme 19.

Under the above mentioned conditions, bromobenzene has been coupled with imidazole, 4-methylimidazole, pyrazole, and benzimidazole giving 92%, 91%, 92%, and 90% yields, respectively.

Easily prepared (*S*)-pyrrolidinylmethylimidazoles were also suggested as ligands for catalytic *N*-arylation of azoles; the best results were obtained with **18** (Scheme **20**) [27].

For imidazole arylation, only bromo- and activated chloroarenes were investigated. The yields were very good; for coupling of 4-bromobenzonitrile and 4-bromoanisole with imidazole, the yields were 95 and 88%, respectively; but in the case of the ethyl ester of 4-

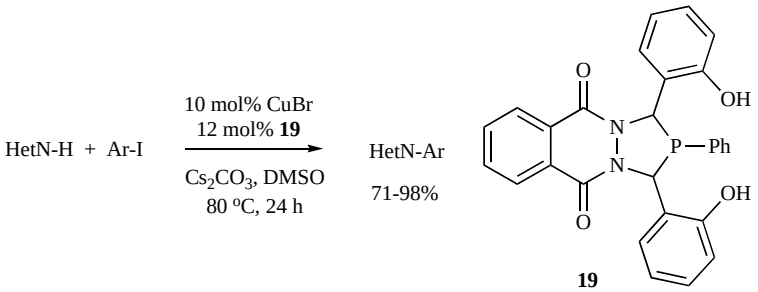


Scheme 20.

bromobenzoic acid, the yield was 61%. Although the author did not discuss it, this fact seems to be due to partial ester group hydrolysis, as observed in almost all of the above mentioned methods. Heteroarylhalogenides can also used as substrates in this method, for example, 2-bromopyridine with imidazole gave product in 98% yield.

Benzimidazole, pyrazole, and even 2-(1*H*-imidazol-2-yl)-1*H*-imidazole have been selectively monoarylated by bromobenzene using the CuI/**18** system, with 75%, 87%, and 62% yields, respectively. 1,2,4-Triazole gave a very low yield with bromobenzene, but can be arylated with iodobenzene at 90 °C in 96% yield [27].

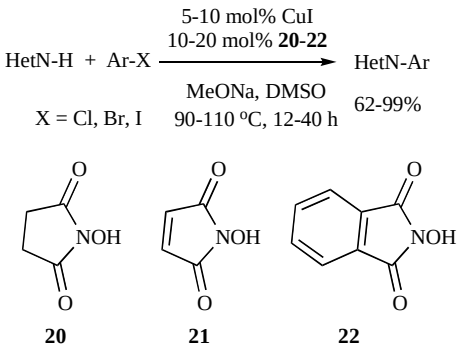
A diazaphospholane **19** racemic mixture was suggested as a ligand for the CuBr catalyzed arylation of amines and some azoles with iodobenzenes (Scheme **21**) [28].



Scheme 21.

The main advantages of the proposed system are lower reaction temperatures compared to the most cited methods above and lower ligand loading. Under the proposed conditions, imidazole, pyrazole, and benzimidazole were arylated with iodobenzene in 98%, 95%, and 78% yields, respectively. The substrate scope of this ligand was comparable to others suggested for *N*-arylation.

Jiang's group has introduced a series of *N*-hydroxyimides **20**-**22** as ligands for CuI in the coupling of azoles with chloro-, bromo-, and iodoarenes (Scheme **22**) [29].

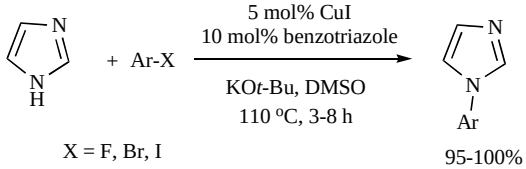


Scheme 22.

The main peculiarity of this proposed system was using a much stronger base, sodium methoxide. Imidazole, 2-ethylimidazole, and benzimidazole were investigated as substrates. Mainly electron-deficient chloroarenes were used, but even in this case, yields were only moderate. For example, the reaction of imidazole and 4-nitrochlorobenzene produced a 62% yield; if 2-chlorobenzonitrile was used, the yield dropped to 52%. Also, imidazole in reaction with iodobenzene, 4-bromoanisole, and 2-bromopyridine gave corresponding products with 98%, 88%, and 96% yields. The main question not answered by authors is the ligand selection criteria for each particular case.

The most exciting finding was that azoles can catalyze *N*-arylation of other azoles. Verma's group has suggested using benzotriazole as a ligand for arylation of imidazoles with aryl and heteroaryl halides (Scheme **23**) [30].

A distinctive feature of this method is achievement of excellent yields of products even with sterically hindered arenes. Thus, imidazole, in reaction with 2-iodotoluene and 2-iodoanisole, gave products with 92% and 93% yields, respectively, and in reaction of benzimidazole with 2-iodotoluene, the yield was 93%. Another feature of this method is reduced reaction times ranging from 3 to 8 h compared to other methods. Finally, the possibility of coupling imidazole with electron-deficient fluoroarenes was demonstrated. Coupling with 1-fluoro-2-nitrobenzene and 2-fluorobenzonitrile, gave yields of 100% in both cases; however, it is possible that there is not a catalytic, but instead a simple S_NAr substitution of fluorine by the imidazolide anion generated in highly basic conditions.

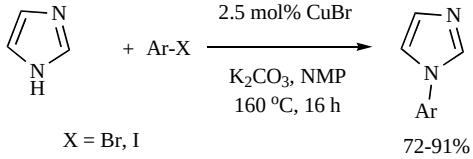


Scheme 23.

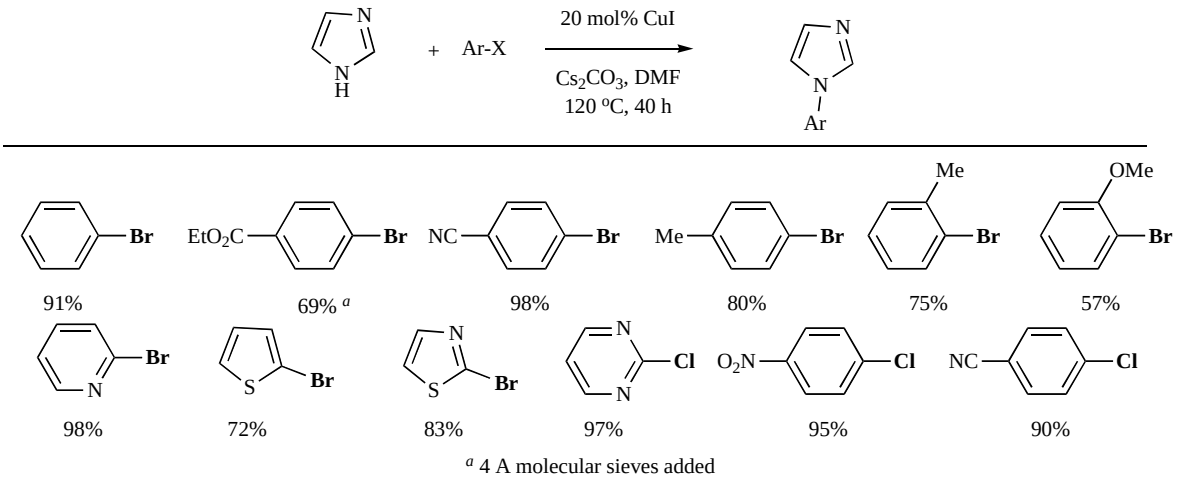
As in case of Cu_2O, one of the exciting questions is whether it is possible to conduct *N*-arylation with copper salts without additional ligands. By the end of 2007, several authors reported progress in this field.

One of the first reports demonstrating coupling of azoles with iodoarenes was published by Chan's group. They used 5 mol% CuI as catalyst, 5 mol% *n*-tetrabutyl ammonium bromide as phase-transfer catalyst, and NaOH in refluxing toluene, for coupling imidazole and indazole with iodobenzene (22 h), giving 84% and 50% yields, respectively [31].

van Koten's group investigated three copper (I) salts, CuCl, CuBr and CuI, as catalysts in the coupling of some iodo- and bromoarenes with imidazole in ligand-free conditions; the best results were obtained with CuBr (Scheme **24**) [32].



Scheme 24.



[a] 4 A molecular sieves added

Scheme 25.

Despite the harsh conditions employed, the yield of products was very good, although only four haloarenes were investigated. Reaction of imidazole with iodo-, bromobenzene, 4-bromotoluene, and 4-bromoanisole led to the corresponding products with 72, 84, 89, and 91% yields.

Up to the present time, the most in-depth investigation in this field was published by You's group. They have suggested a system allowing for coupling of a wide range of azoles with aryl and heteroaryl halides (Scheme **25**) [33].

Besides imidazole, benzimidazole, pyrazole, 3,5-dimethylpyrazole and 1,2,4-triazole were investigated. In addition, 4-Methyl-1*H*-imidazole produced a mixture of 1-phenyl-4-methyl- and 1-phenyl-5-methylimidazole in a 4.3:1 ratio with bromobenzene; similarly, 3-methyl-1*H*-pyrazole with iodobenzene afforded a mixture of 1-phenyl-3-methylpyrazole and 1-phenyl-5-methylpyrazole (3:1).

Summarizing the use of copper(I) as catalyst for azole arylation, the following can be said: at the moment this type of reaction is the most effective, universal and perspective in contrast to other ones, although some shortcomings exist: 1) limited range of aryl halides tried, for the most part only iodo- and bromo-derivatives, although in some papers possibilities of arylation with chloro- and even fluoroarenes showed, these are still isolated cases; 2) lowering the product yield in the presence of *ortho*-substituents to the reaction center; 3) complications from hydrolysis of functional groups (–CN, -COOR, etc.) sensitive to bases; 4) formation of an isomer mixture during arylation of asymmetric azoles.

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