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Transition metals in the amination of chloroarenes

O V Serdyuk, V T Abaev

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Abstract. The review is devoted to the catalytic amination of chloroarenes and chlorohetarenes. Examples of the formation of the C—N bond in the presence of iron-, nickel- and copper-based catalytic systems are given. The bibliography includes 96 references.

I. Introduction

The role of aromatic and heteroaromatic amines in modern pharmacology,[1] agriculture,[2] photo- and copying technologies [3,4] is difficult to overestimate. They are used in the synthesis of natural compounds and polymers,[5,6] conducting materials and their precursors; certain examples are shown in the next page.[7,8]

It is not surprising that the paramount industrial importance of chemistry of aromatic amines requires more sophisticated synthetic methods. Recently, books [9,10] and a review [11] have been published that covered modern methods of arylamine synthesis. The present review considers the amination reactions catalyzed by transition metals and their compounds.

In reactions of the C—N bond formation, palladium was used most widely as a catalyst that allows the C—C, C—N, C—O, C—S cross-coupling reactions to be carried out under mild conditions and with high efficiency. A considerable contribution to this line of research was made by Buchwald and Hartwig with their coworkers who dealt with palladium catalysts (*e.g.*, see Refs 12 and 13). However, the high cost of palladium and the fact that in industry preference is given to heterogeneous processes have stimulated the search for new catalysts based on other, cheaper and more accessible transition metals.

The catalysis by palladium complexes was discussed in detail in a review.[14] In addition, reviews devoted to reactions of new C—N bond formation catalyzed by palladium and nickel complexes,[15,16] cross-coupling reactions of chloroarenes in the presence of palladium,[17] palladium-catalyzed reactions of aryl halides with amines in industry [18] were published. A general survey of patented technologies of cross-coupling [19] and reviews of the C—N and C—O couplings [20,21] have appeared.

In the present review, attention is focused on the examples of the C—N bond formation in the presence of iron, nickel and copper, their compounds and complexes, *i.e.*, to amination and amidation of haloarenes and N-arylation of heterocycles.

Transition metals are known to play an important role in the synthesis of heterocyclic compounds and their functionalization.[22] Thus intramolecular catalytic amination reactions can be used in constructing the heterocyclic framework. Like intermolecular reactions, they proceeded faster and under milder conditions on microwave irradiation.[23] However, publications describing the reactions under microwave radiation are less common and beyond the scope of the present review.

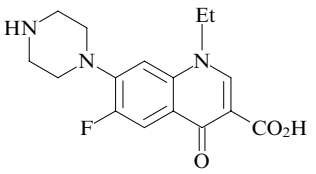
The impressive number of publications on this subject made us to restrict our consideration chiefly to examples of amination of the most available and cheapest substrates, namely, chloroarenes [24] and their heterocyclic analogues. The majority of cited studies were published in 2000 – 2008.

II. Catalysis by iron and cobalt compounds

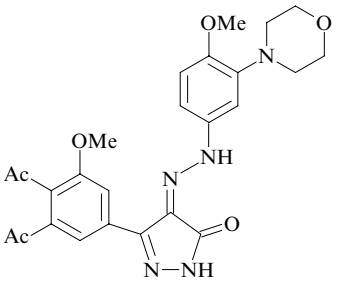
Iron as the catalyst has for a long time been in the shadow of other transition metals. Catalysts based on it were used in cross-coupling reactions rather seldom (for details of reactions in the presence of iron-containing catalysts, see a review [25]). Despite their certain advantages (low cost, acces-

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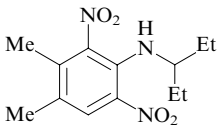
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Uspekhi Khimii **78** (11) 1113 – 1128 (2009); translated by T Ya Safonova



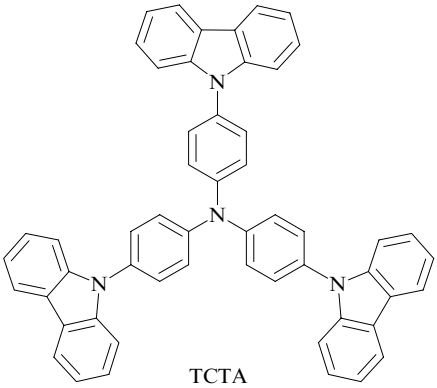
Norfloxacin is an antibacterial agent



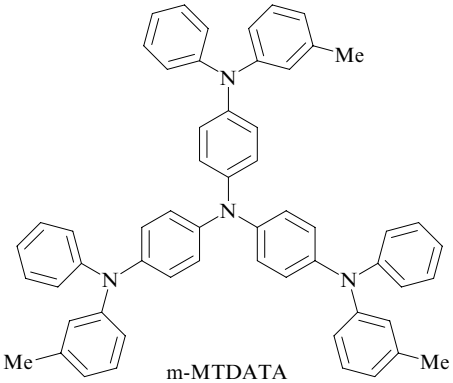
A potential drug to treat diabetes and Alzheimer's disease



Pendimethalin is a selective herbicide



TCTA

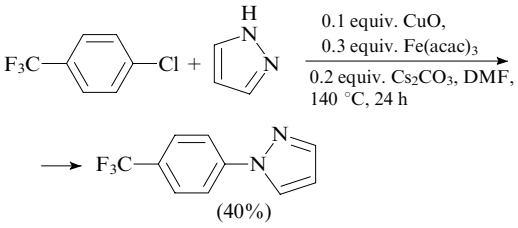


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Materials for manufacturing thermally stable electroluminescent devices

sibility and environmental safety), it was only recently that iron compounds and complexes have been recognized as a serious alternative to other catalysts (see reviews [26–28]). At present, only a few examples of N-arylation of azoles in the presence of iron compounds are known.[29–31]

Thus iodo-, bromoarenes and 4-trifluoromethylchlorobenzene reacted with pyrazole, imidazole, 1,2,4- and 1,2,5-triazoles, indole in the presence of copper(II) oxide and $Fe(acac)_3$; for example,[29]



The yields in this reaction are 40%–98%, it was not accompanied by the formation of side products, *i.e.*, arenes and biaryls. It is noteworthy that the reaction did not occur in the absence of either component of this bimetallic catalyst. However, the use of *N*,*N*-dimethylethylenediamine as the additive to $FeCl_3$ or Fe_2O_3 allowed carrying out the reaction of azoles with iodo- or bromoarenes in the absence of the copper co-catalyst.[30] The reaction mechanism is not clear yet.

Cobalt salts are ineffective as the catalysts of amination of chloroarenes. Thus in the presence of cobalt(II) chloride at 210 °C over a period of 6 h, only 5% of chlorobenzene reacted with dimethylamine (1% reacted in the absence of the catalyst).[32] Under analogous conditions, bromobenzene gave the product in ~62% yield.

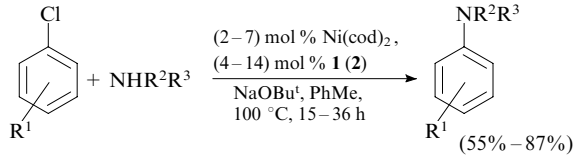
III. Catalysis by nickel and its compounds

1. Reactions of chloroarenes with secondary aliphatic and aromatic amines

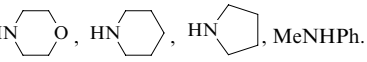
Nickel-based catalysts have firmly occupied their niche in synthetic organic chemistry. They were widely used in asymmetric synthesis, cycloisomerization, cyclooligomerization, carbonylation, cross-coupling reactions.[33]

As early as in 1950, in studies on the activity of copper or other metal catalysts in the reaction of chlorobenzene with methylamine it was assumed [34] that nickel salts could also serve as efficient catalysts of various reactions of haloarenes including amination. Indeed, the yield in the reaction of chlorobenzene with dimethylamine for 6 h at 210 °C in the presence of $NiCl_2$ was 68%.[32] At the same time, the rather severe conditions of this reaction and its low efficiency restricted its application field for a long period. The discovery of new palladium-based catalytic systems, particularly, trialkylphosphine palladium complexes for the amination of chloroarenes revived the interest of synthetic chemists in nickel catalysts.

The first example [35] of amination of chloroarenes in the presence of nickel complexes was reported in 1997. Thus the reaction of chloroarenes in secondary aromatic and aliphatic amines proceeded in good yields in the presence of catalytic amounts of $Ni(cod)_2$ (cod is cycloocta-1,5-diene) and 1,1′-bis(diphenylphosphino)ferrocene (dppf, **1**). This reaction is similar to amination in the presence of palladium complexes with the corresponding ligands that stabilize the metal in the zero oxidation state and favour the oxidative addition.[14] Under these conditions, primary amines afforded large amounts of side products, namely, imines and arenes due to β-hydride elimination.

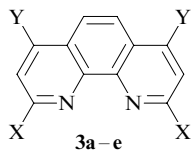


R^1 = 4-Me, 4-MeO, 2,5-Me_2, 4-CN;

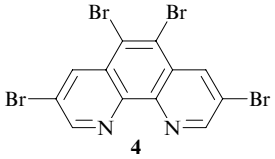
R^2R^3NH = , MeNHPh.

Chlorohetarenes HetCl (*e.g.*, Het = 3-Py, 4-Py; Py is pyridyl) reacted in the similar way. In place of dppf, 1,10-phenanthroline (phen, **2**) could act as the ligand. Other phosphines, such as PPh_3, $P(o\text{-tol})_3$, 1,3-bis(diphenylphosphino)propane, 1,2-bis(diphenylphosphino)ethane and several other, were shown to be ineffective in this reaction.[35]

It should be noted that the activity of a catalyst based on nickel and a substituted phenanthroline depended on the position of substituents in the ligand aromatic system rather than on their nature. Thus in this reaction, phenanthrolines **3a**,**b** and 5,6-methylenedioxyphenanthroline containing electron-donating groups in their pyridine fragments produced the results similar to those observed for unsubstituted phenanthroline (**2**), whereas a catalyst based on phenanthroline **3c** exhibited virtually zero activity. At the same time, nickel complexes with 4,7-diaryl- or 4,7-dihalogen-substituted phenanthrolines (**3d**,**e**) and with phenanthroline **4** surpassed a complex containing unsubstituted analogue **2** in their activity.[36]



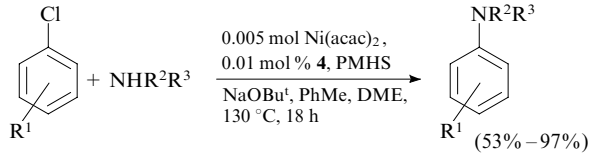
3a–e



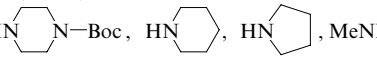
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X = H: Y = OMe (**a**), *N*-Pyr (**b**); X = Me, Y = H (**c**);
X = H: Y = Ph (**d**), Cl (**e**) (Pyr is pyrrolidino).

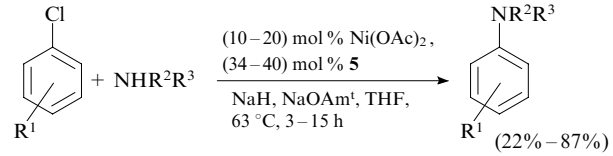
In the presence of small amounts of nickel acetylacetonate, phenanthroline **4** and polymethylhydrosiloxane (PMHS), various chloroarenes reacted with secondary aromatic and aliphatic amines.[36] In these reactions, polymethylhydrosiloxane functioned as a reducing agent, $Ni^{II} \rightarrow Ni^0$.



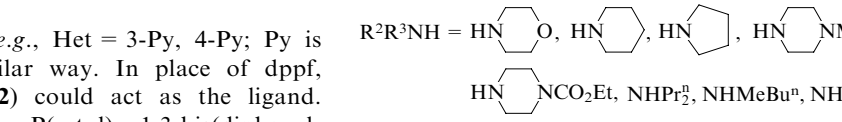
R^1 = 4-Me, 4-MeO, 2-Me, 4-Bz, 4-CF_3, 4-$CH(OCH_2)_2$, 3-CO_2Bu^t, 3-F-2-$CH(OCH_2)_2$;

R^2R^3NH = , MeNHPh, n-$C_6H_{13}NHMe$, Bu_2NH, MeNHBn.

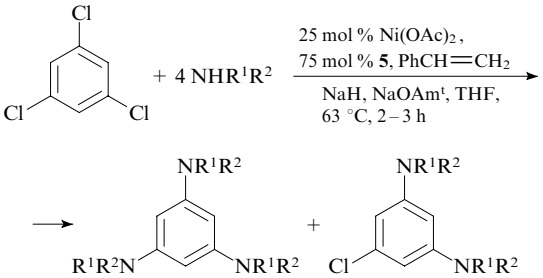
A nickel complex with 2,2′-bipyridine (**5**) can serve as a catalyst.[37–42] In this case, substituted chloroarenes reacted with amines under sufficiently mild conditions.[38] However, the presence of a strong base substantially narrowed the range of functional groups that can be present in the substrate.

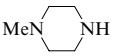
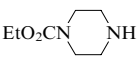


R^1 = 2-Me, 3-Me, 4-Me, 4-MeO, 4-CF_3;

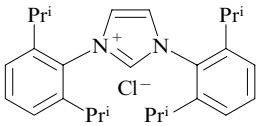
R^2R^3NH = , $NHPr^n_2$, $NHMeBu^n$, $NHMeAm^n$, MeNHBn, Bn_2NH (Am = C_5H_{11}).

Under the mentioned conditions, diarylation of piperazine,[39] amination of 1,3,5-trichlorobenzene and 1,2-, 1,3- and 1,4-dichlorobenzene,[40–42] including selective reactions, proceeded quite easily. For example, the reaction of 1,3,5-trichlorobenzene with 2 mol of an amine led to the monosubstitution product, whereas the use of 4 mol of the amine afforded mainly 1,3,5-triaminobenzene. The addition of small amount of styrene that reacted with excess hydrogen made it possible to avoid a side reaction, namely, the reduction of the C—Hal bond.

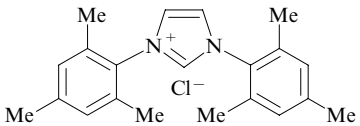


Amine	Ratio products of tri- and disubstituted
	71 : 14
	60 : 7
	75 : 7

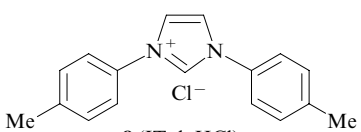
N-Heterocyclic carbenes (nhc) can be used as the ligands that stabilize Ni^0 and facilitate the reaction, their precursors are imidazolium salts **6**–**14**.



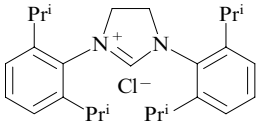
6 (IPr·HCl)



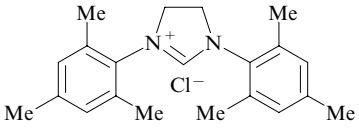
7 (IMes·HCl)



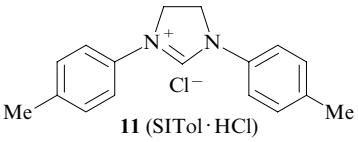
8 (ITol·HCl)



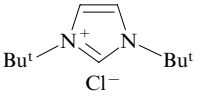
9 (SIPr·HCl)



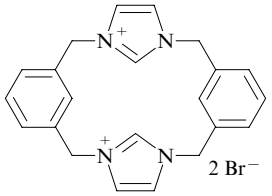
10 (SIMes · HCl)



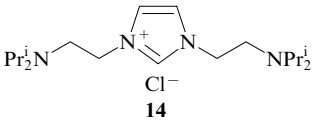
11 (SITol · HCl)



12

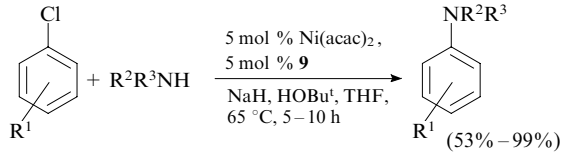


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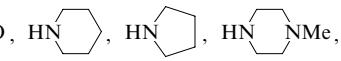


14

A catalyst based on a Ni^0 complex with the SIPr · HCl ligand (**9**) exhibited the highest activity in the amination. In the presence of this catalyst, substituted chloroarenes reacted with secondary aliphatic amines with the highest efficiency.[43,44] The catalyst was generated *in situ* from $Ni(acac)_2$, an imidazolium salt, *tert*-butyl alcohol and sodium hydride. The latter reacted with Bu^tOH to afford the alkoxide $NaOBu^t$, which deprotonated the imidazolium salts nhc · HCl and reduced Ni^{II} to Ni^0.

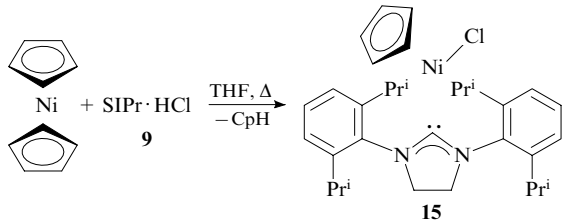


R^1 = 2-Me, 3-Me, 4-Me, 3-MeO, 4-CN, 4-Bz;

R^2R^3NH = 

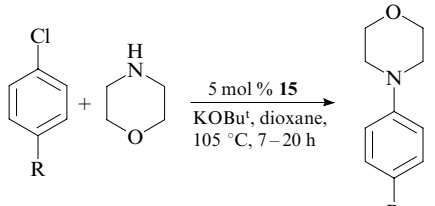
MeNHBn, Bn_2NH, $MeNHCH_2CH(OMe)_2$.

Heating under reflux of nickelocene and imidazolium salt **9** in tetrahydrofuran smoothly affords complex **15**, which can serve as the amination catalyst.



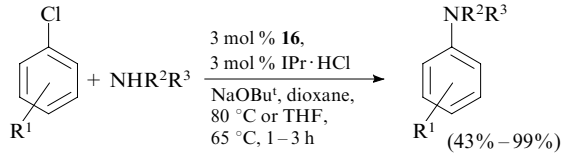
15

Presumably, the driving force of the reaction was the formation of the Ni—Cl bond, because an analogous reaction failed to proceed with tetrafluoroborate (nhc · HBF_4). In the system dioxane – $KOBu^t$ – **15** at 105 °C, *p*-chlorobenzonitrile reacted with morpholine for 7 h to give the corresponding amino derivative in 82% yield.[45]

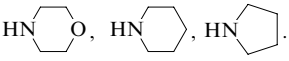


R = CN (82%), Me (48%).

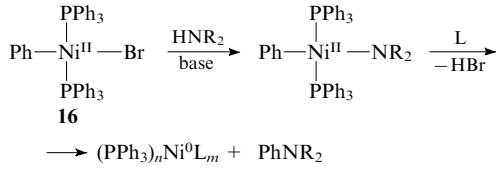
A complex catalyst comprising IPr · HCl (**6**) and $Ni(PPh_3)_2(Ph)Br$ (**16**) proved more efficient in reactions of chloroarenes with cyclic alkylamines.[46] In the presence of this catalyst, no additional reduction was required and the transformation took 1 – 3 h.



R^1 = H, 2-Me, 4-Me, 4-Bz, 4-Cl;

R^2R^3NH = 

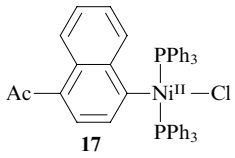
Such σ-aryl Ni^{II} complexes are easily accessible (from $NiCl_2 \cdot H_2O$)[47] and convenient in handling being resistant to air and moisture. The following mechanism of activation of this complex was assumed.



L = IPr · HCl (**6**).

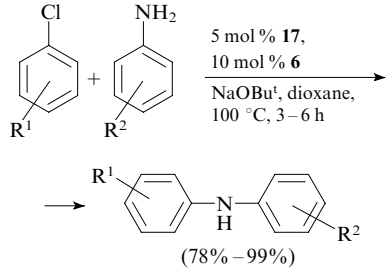
2. Reactions of chloroarene with primary aromatic amines

Nickel complex **17** (an analogue of complex **16**) effectively catalyzed the reaction of chloroarenes with aromatic amines.



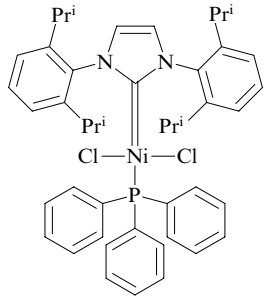
17

With this catalyst, the reaction proceeded for 3 h in virtually quantitative yields.[46]



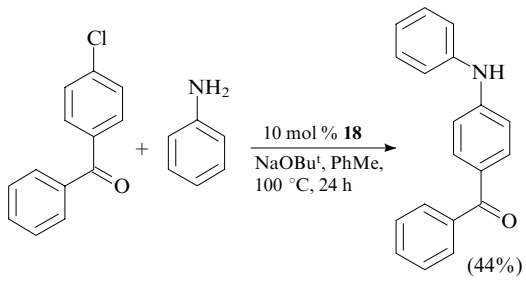
R^1 = H, 2-Me, 4-Me, 4-Bz; R^2 = H, 4-Me, 4-MeO, 3-Me, 2,6-Me_2.

Nickel complex **18** was somewhat less active;

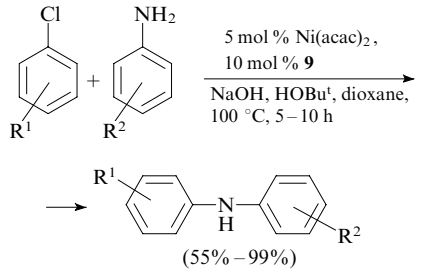


18

it catalyzed the reactions of bromoarenes and activated chloroarenes (*e.g.*, *p*-chlorobenzophenone) with aniline.[48] This catalyst is easily accessible and stable in air.

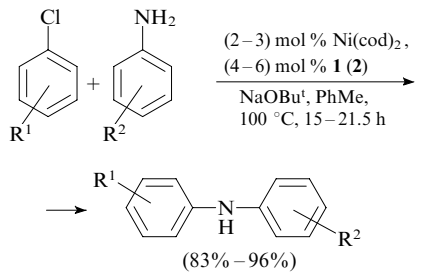


Amination in the presence of the Ni^0–SIPr complex proceeded with higher efficiency with the exception of certain *ortho*-substituted anilines, for instance, *o*-anisidine. Incomplete transformation could in this case be explained by the reduction of the catalyst activity due to the coordination of nickel to the oxygen and nitrogen atoms of the arylamine.[44] In this reaction, one should maintain the ratio ligand : metal = 2 : 1 with small excess of the amine and use dioxane as the solvent.



R^1 = H, 2-Me, 3-Me, 4-Me, 3-F, 2,5-Me_2;
R^2 = H, 4-Me, 2-Et, 2,4,6-Me_3, 2,6-Pr^i_2, 3-MeO, 4-MeO, 3-F, 2-F.

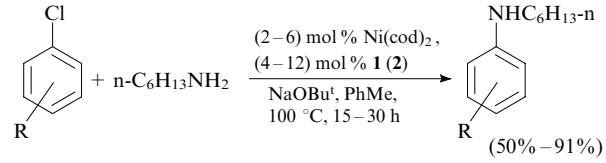
The systems $Ni(cod)_2$–dppf and $Ni(cod)_2$–phen catalyze the reactions of chloroarenes with aromatic amines with equal efficiency.[35]



R^1 = 4-Me, 4-MeO, 2,5-Me_2, 4-CN; R^2 = 2-Me, 4-Me, 4-MeO.

3. Reactions of chloroarenes with primary aliphatic amines and benzophenonimine

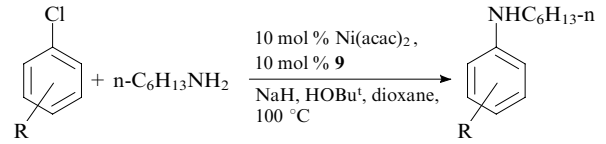
In the presence of catalytic amounts of $Ni(cod)_2$ and dppf (**1**) or phenanthroline (**2**), chloroarenes reacted with n-hexylamine giving the reaction products in yields from moderate to high.[35]



R = 2,5-Me_2, 4-Bz.

The reaction of 3-chloropyridine and substituted bromo- and iodoarenes with benzopheno imine proceeded in a similar fashion.[49]

The reaction of activated chloroarenes with primary aliphatic amines was catalyzed by the Ni^0–SIPr complex. The reaction with unsubstituted chlorobenzene proceeded more slowly. The low yield of products in the case of alkylamines was explained[44] by the formation of non-reactive bisamino- or bisamido-bridged nickel complexes.

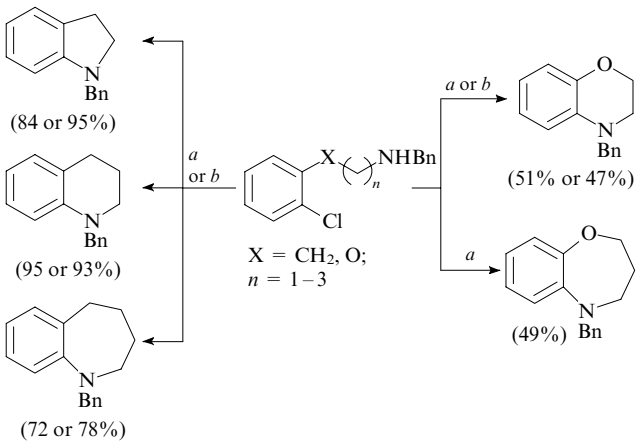


R = Bz (65%), H (37%).

4. Intramolecular amination reactions in the synthesis of heterocycles

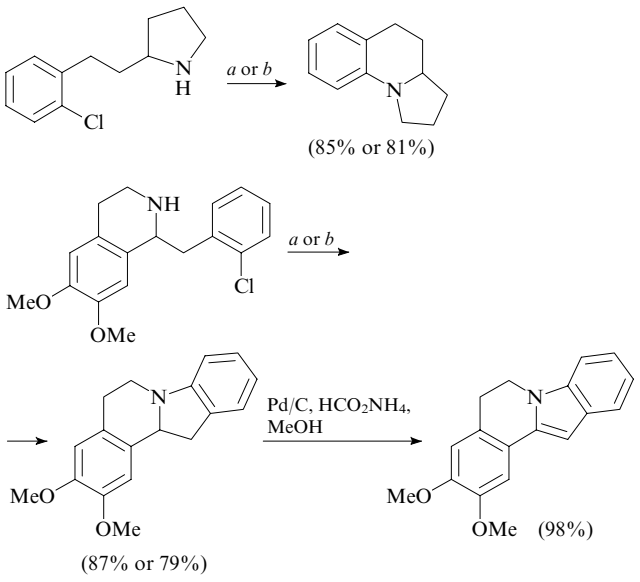
Intramolecular catalytic amination can be used in the synthesis of *N*-heterocycles, namely, dihydroindoles, tetrahydroquinolines, tetrahydrobenzazepines as well as tetrahydrobenzoxazines and tetrahydrobenzoxazepines. In this case, nickel complexes with 2,2′-bipyridine (**5**) or SIPr served as the catalysts (Scheme 1).[50]

Scheme 1



(*a*) 5 mol % Ni^0, 15 mol % **5**, 1 mol % NaOBu^t, 9.5 mol % NaH, 5 mol % $PhCH{=}CH_2$, THF, 65 °C;
(*b*) 2 mol % Ni^0, 2 mol % SIPr, 15 mol % NaOBu^t, dioxane, 100 °C.

This method made it possible also to synthesize benzo[*e*]indolizines and 5,6-dihydroindolo[2,1-*a*]isoquinolines.[50]



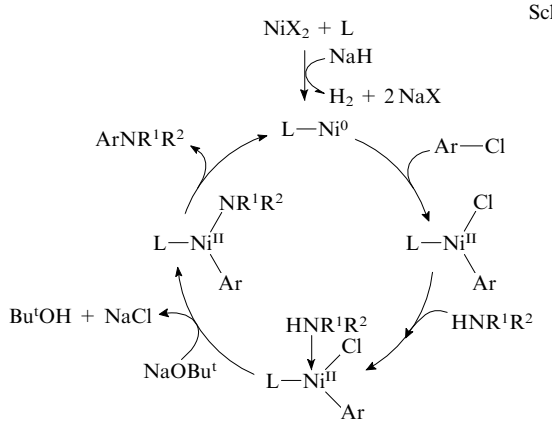
(*a*) 5 mol % Ni^0, 15 mol % **5**, 1 mol % $NaOBu^t$, 9.5 mol % NaH, 5 mol % $PhCH{=}CH_2$, THF, 65 °C, 5 h;
(*b*) 2 mol % Ni^0, 2 mol % SIPr, 15 mol % $NaOBu^t$, dioxane, 100 °C, 6 h.

5. The mechanism of amination

The mechanism of amination of chloroarenes in the presence of nickel complexes is similar to that of palladium-catalyzed amination.[14] However, the activity of Ni^0 complexes was considerably higher as compared with Pd^0 complexes.[24]

According to modern concepts, the first stage of the catalytic cycle includes the formation of active Ni^0 catalyst species and their coordination to the ligand. Electron-donating properties of the latter favour the oxidative addition of chloroarene to Ni^0, *i.e.*, the second stage, after which transmetallation (the third stage) occurs. In turn, the steric characteristics, particularly, bulkiness of the ligand favoured the reductive elimination (the final stage) (Scheme 2).[44]

Scheme 2



Ar = Ph, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 4-NCC_6H_4, 2-Py, 3-Py, 3-ClC_6H_4, *etc.*;

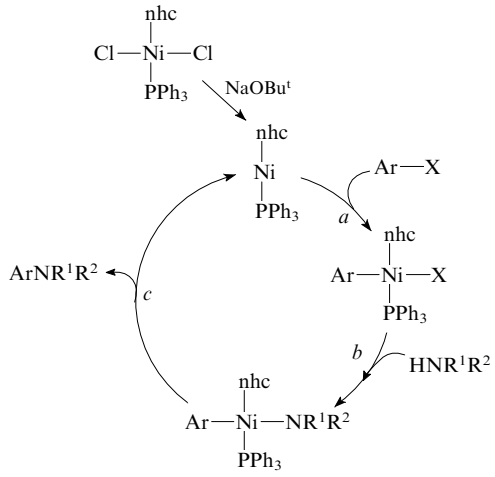
R^2R^3NH = HN⟨O⟩, HN⟨⟩, HN⟨⟩, HN⟨⟩, HN⟨NMe⟩,

MeNHBn, Bn_2NH, $MeNHCH_2CH(OMe)_2$.

X = acac; L are ligands **6**–**14**.

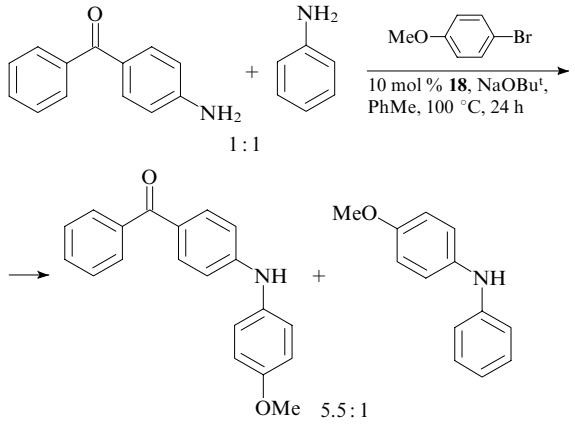
For complex **18**, the oxidative addition (stage *a*) proceeded quickly due to the high activity of Ni^0 species and did not affect substantially the reaction rate (Scheme 3).[48]

Scheme 3



nhc = **18**; Ar = RC_6H_4 (R = H, 4-MeO, 4-Bz, 4-CF_3); X = Cl, Br; R^1-R^2 = $(CH_2)_2O(CH_2)_2$; R^1 = H: R^2 = 2,4,6-$Me_3C_6H_2$, 2-$Pr^iC_6H_4$, 2,6-$Pr^i_2C_6H_3$, Ph, 4-ClC_6H_4, 4-$F_3CC_6H_4$, 4-$MeOC_6H_4$; R^1 = R^2 = Ph.

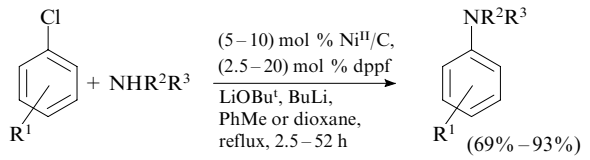
In contrast to the palladium-catalyzed amination, the relationship between the amine basicity and the yield of the amination product was observed. Thus less basic amines reacted with haloarenes to give higher yields of the products, which stressed the role of transmetallation in the catalytic cycle (stage *b*).[48]



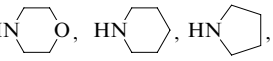
6. Heterogeneous catalyst Ni^0/C: synthesis, transformations and mechanism of catalysis

In certain cases, as the alternative to homogeneous palladium catalysts, one can use nickel on charcoal (Ni^0/C) heterogeneous catalyst, which also enables reduction of chloroarenes and Negishi, Kumada and Suzuki coupling reactions.[51] The catalyst was prepared by the reduction of 5% – 10% $Ni(NO_3)_2$/C with butyllithium.

In the presence of Ni/C and dppf (**1**) as a ligand, chloroarenes reacted with primary and secondary aromatic amines.[52] No reaction was observed with imidazole and aza-crown ethers.



R^1 = 4-Me, 4-MeO, 4-Bz, 4-CN, 2-Me-5-F;

R^2R^3NH = , Bn_2NH, n-$C_6H_{13}NH_2$,

4-$MeC_6H_4NH_2$, 2-$MeC_6H_4NH_2$, $PhNH_2$.

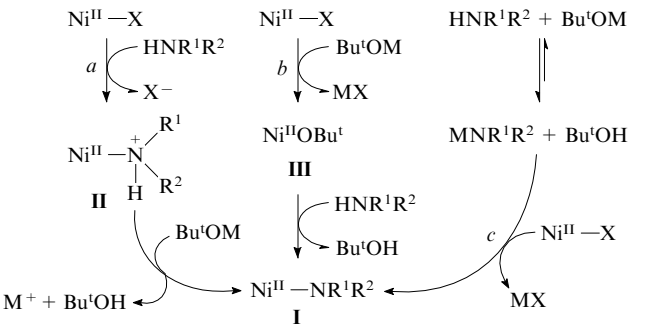
In the majority of cases, it was sufficient to employ 5 mol % of the catalyst and 2.5 mol % of phosphine **1**. High boiling toluene and dioxane should be preferred to THF as the solvent. The reaction is known to proceed more easily with lithium alkoxides than with sodium and potassium alkoxides. Other bases proved to be ineffective in this reaction. The catalyst was easily removed by filtration and, after the completion of the reaction, the solution contained only traces of nickel, which was especially important in the industrial-scale synthesis of drugs.

It should be noted that with the increase in the nickel content on the charcoal support, the degree of conversion of chloroarenes decreased. The reduction of Ni^{II}/C with hydrogen to afford reactive Ni^0/C species proceeded at 425 °C and also reduced the catalyst activity. The use of Bu^nLi made it possible to decrease the temperature of the $Ni^{II}/C \rightarrow Ni^0/C$ reduction and increase the catalyst activity as compared with the Ni^0/C species prepared at 425 °C. How can we explain this dependence?

It was found [53] that homogeneous nickel species took part in the catalytic cross-coupling cycle, *i.e.*, during the reaction, nickel partly passed from the solid charcoal support to solution. Its content in solution somewhat increased when the reaction mixture was heated and Ni^{II}/C was reduced with Bu^nLi. The reduction with hydrogen produced coarser nickel particles for which it was more difficult to pass into solution. The higher nickel content on the charcoal surface led to blocking of pores, which also hindered the migration of Ni particles to solution and decreased the catalyst activity.

The $Ni^{II}/C \rightarrow Ni^0/C$ reduction could proceed as a result of a reaction of a metal *tert*-butoxide with an amine in the absence of Bu^nLi; however, in this case it took several minutes (the induction period) for the reaction to proceed. The key Ni^{II} **I** amide complex can be formed by different routes (Scheme 4).

Scheme 4



M = Li, Na, K.

Pathway *a* includes the formation of a Ni^{II} complex with amine (**II**) followed by its deprotonation; pathway *b* implies the preliminary formation of a Ni^{II} complex with the *tert*-butoxide ion (**III**), deprotonation of the amine and its reaction with complex **III**. According to pathway *c*, the rate-determining step is the reaction of amine with metal *tert*-butoxide to form metal amide MNR^1R^2 which is subsequently complexed with Ni^{II} (**I**). It was found experimentally that of three possible versions, the reaction rate was determined by amine deprotonation and complexation with compound **III** (pathway *b*).[54]

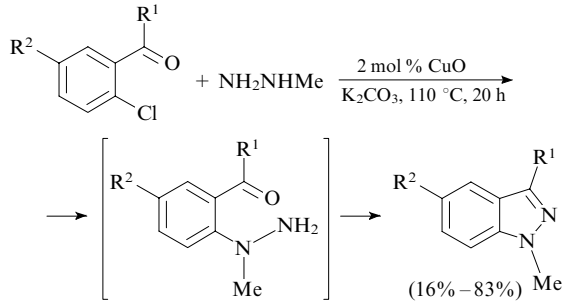
IV. Catalysts based on copper and its compounds

Cross-coupling reactions to form new C—C, C—N, C—O, C—S bonds in the presence of copper have been known for more than a century. Thus the already classical Ullmann condensation (synthesis of diarylamines by the reaction of aryl halides with aromatic amines) was discovered in 1903. However, drastic conditions of this reaction, namely, high temperature, the presence of strong bases and the use of stoichiometric amounts of copper or its salts did not favour its wide application. The revived interest in the Ullmann condensation was associated with the progress in the chemistry of palladium, the elaboration of new palladium-based catalytic systems, the synthesis of new ligands and the detailed studies of the mechanism of different cross-coupling reactions. Several reviews were devoted to the modern synthetic methods of the formation of new C—N, C—O, C—S bonds in the presence of copper.[55–59] Despite rapid progress in this field, the majority of amination reactions in the presence of copper catalysts concerned iodo-and bromoarenes, while the amination reactions of chloroarenes were less abundant.

1. Reaction of chloroarenes with ammonia and hydrazines

The ability of chloroarenes to react with amines and ammonia in the presence of copper has been known for a long time. Thus chlorobenzene reacts with ammonia in the presence of copper(I) salts (CuI, CuCl). The latter exhibited the higher activity in this reaction than copper(II) salts.

Copper(II) oxide can act as the catalyst. Thus in its presence, *N*-methylhydrazine reacted with 2-chloroaryl ketones and substituted *o*-chlorobenzoic acids and played the role of both the amination agent and the solvent. The subsequent spontaneous intramolecular cyclization of the arylhydrazines formed resulted in 1-methyl-1*H*-indazoles.



R^1 = Me, Ph, OH; R^2 = H, Cl, NO_2, MeO.

The use of more expensive Cu_2O and Cu/CuO gave the same results.[60] Unsubstituted *o*-chlorobenzoic acid is insufficiently soluble in *N*-methylhydrazine; hence, the reaction was carried out in benzene.

2. Reaction of choroarenes with aromatic amines

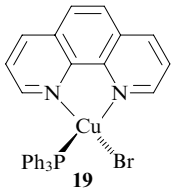
The reaction of *o*-chlorobenzoic acid with aromatic amines in water in the presence of 1 equiv. of K_2CO_3 and 3 mol % of copper-containing catalyst proceeded, as a rule, with high efficiency (Table 1). In this case, Cu_2O, CuI, CuOAc, Cu_2SO_4 could serve as the copper source.[61]

The reaction could also be carried out in butanol, ethylene glycol and ethoxyethanol. Amination in ethoxyethanol was catalyzed most efficiently by Cu/Cu_2O. In the series of bases (Na_2CO_3, K_2CO_3, Cs_2CO_3, K_3PO_4, NaOAc, $KOBu^t$, tetramethylpiperidine), the amination product was formed in the highest yield in the presence of potassium and sodium carbonates.[63, 65]

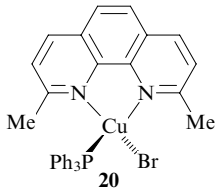
However, from the standpoint of practice, the complex $Cu(py)_2Cl_2$ proved to be more convenient as the catalyst because it allowed amination of *o*-chlorobenzoic acid with sufficiently high efficiency in the absence of inert atmosphere (see Table 1).[64]

The amination of haloarenes in the presence of atmospheric oxygen was also efficiently catalyzed by CuO nanoparticles (Aldrich, particle size 33 nm). The reaction of chlorobenzene with aniline in DMSO in the presence of KOH and CuO nanoparticles carried out at 110 °C for 18 h afforded diphenylamine in 60% yield. Under these conditions, conventional copper oxide and copper(II) salts afforded the amination product in lower yields.[66]

Complexes **19** and **20** resistant to air and moisture and soluble in many organic solvents (dichloromethane, chloroform, toluene, benzene, DMF, DMSO) proved to be equally practical.[67]

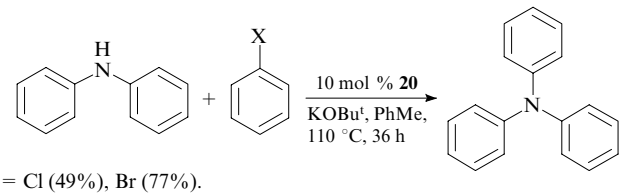


19



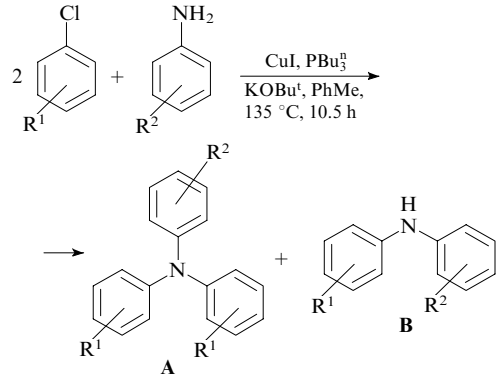
20

Complexes **19** and **20** catalyzed the reaction of haloarenes with secondary aromatic amines; however, for chlorobenzene, the reaction proceeded with low efficiency. Other bases such as K_3PO_4, K_2CO_3, CsF, NaOMe, NaH were not effective under the given conditions.



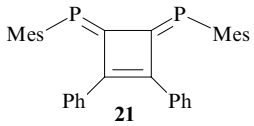
X = Cl (49%), Br (77%).

The system $CuI-PBu^n_3$ proved to be one of the most effective catalysts for the amination of chloroarenes. In the presence of $CuI-PBu^n_3$ and $KOBu^t$ in toluene, the reaction of substituted chloroarenes with primary aromatic amines proceeded with high efficiency. The conversion was incomplete only with *p*-nitroaniline as a weak nucleophile and *p*-nitrochlorobenzene.[68]



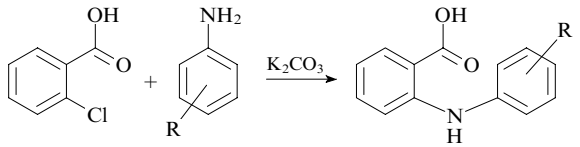
R^1, R^2	Yield (%)	
	A	**B**
H, 2- Me, 4-MeO	80–87	2–5
4-NO_2	29–41	8–11

Diphosphine **21** can serve as the ligand.



21

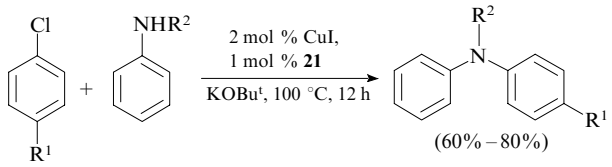
Table 1. Reaction of *o*-chlorobenzoic acid with aromatic amines.



R	Catalyst	Solvent	*T*/°C	*t*/h	Yield (%)	Ref.
4-Me, 3-NO_2, 3-Cl, 4-NO_2, 4-MeO, 4-SO_3H	3 mol % Cu_2O	H_2O	100	5	9–89	61
See [a]	3 mol % Cu	H_2O	100	6	64	62
H, 2-Me, 3-Me, 2-Pr^i, 2-Bu^t, 3-Bu^t, 2-Ph, 4-MeO, 4-NO_2, 3-Cl, 4-CO_2H, 3,5-Me_2, 2,6-Me_2, 2,3-benzo	9 mol % Cu/4 mol % Cu_2O	$EtOCH_2CH_2OH$	130	24	65–99	63
H, 4-Me, 4-MeO, 4-NO_2, 4-CO_2H, 4-CN, 3-Cl, 3-Br, 2,3-benzo	10 mol % $Cu(py)_2Cl_2$	$HOCH_2CH_2OH$	130	24	56–84	64

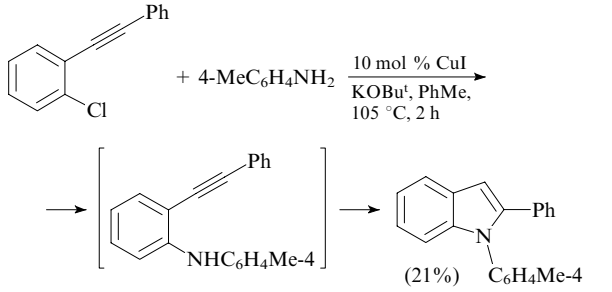
[a] Amine is 2-aminopyridine.

Thus the reactions of chlorobenzene and *p*-chlorotoluene with aniline or *N*-methylaniline in the presence of the CuI – **21** – Bu^{t}OK system afforded amination products in high yields. The reaction was carried out in the absence of solvent; chloroarenes played the role of solvent.[69]



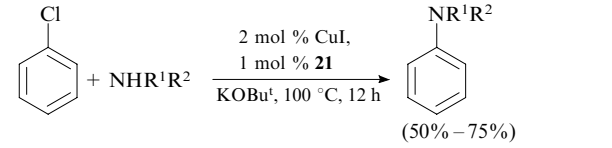
R^1, R^2 = H, Me.

Amination of *o*-alkynylhaloarenes followed by intramolecular cyclization of the amino derivatives formed produced substituted indoles. This reaction proceeded in toluene in the presence of KOBu^t and catalytic amounts of CuI; the yields were 53% – 84% from *o*-alkynylbromoarenes. For the chloro derivative, the reaction took a longer time and was accompanied by the formation of side products, which reduced the indole yield.[70]



3. Reactions of chloroarenes with aliphatic amines

The reaction of chlorobenzene with primary and secondary cyclic alkylamines could be carried out under solvent-free conditions in the presence of the CuI – **21** – KOBu^t system.[69]



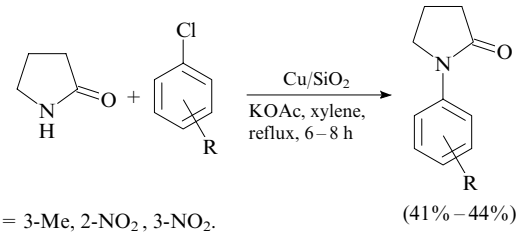
R^1R^2NH = HN⟨O⟩, HN⟨⟩, $Ph(CH_2)_2NH_2$.

Copper-containing hydrotalcites Cu/Al-HT (Cu : Al = 2.5 : 1), *i.e.*, layered materials with the composition $[M^{II}_{1-x}M^{III}_x(OH)_2]A^{n-}_{x/n} \cdot y\,H_2O$ (M^{II} and M^{III} are cations of bi- and trivalent metals Cu^{2+}, Mg^{2+} and Al^{3+}; the role of counter ions (A) can be played by OH^-, Cl^-, NO_3^-, CO_3^{2-}, *etc.*) are useful heterogeneous catalysts of amination. In the presence of Cu/Al-HT, the activated chloroarenes reacted with aliphatic amines. The reaction proceeded at 160 °C in *N*-methylpyrrolidone or in the absence of solvent; the role of the latter was played by the amine. The yields were in the range 45% – 93%, the reaction time was 6 – 16 h.[71]

4. Reaction of chloroarenes with amides

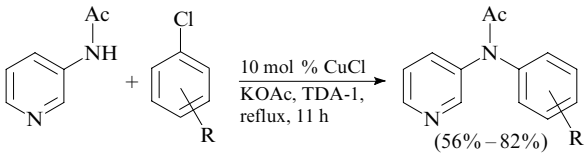
The Goldberg reaction, *i.e.*, copper-mediated N-arylation of amides, was discovered in 1906 following the Ullmann reaction, and for a long time it had a rather narrow scope of applicability for the same reasons. To date, the examples of reactions of chloroarenes with amides are also scarce.

For example, in the presence of Cu on SiO_2 as a catalyst, the reactions of 2(3)-nitrochlorobenzene and 3-chlorotoluene with cyclic amides proceeded with low yields, whereas the reaction with bromobenzene afforded the product in 91% yield.[72]



R = 3-Me, 2-NO_2, 3-NO_2.

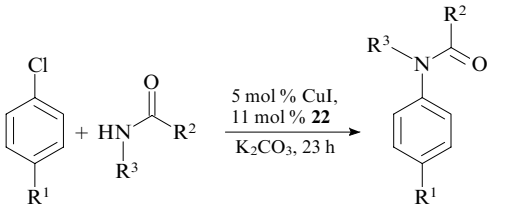
N-Arylation of *N*-(3-pyridyl)acetamide occurred in the presence of catalytic amounts of tris(3,6-dioxaheptyl)amine (TDA-1) and copper(I) with azeotropic distillation of water.[73] Amine TDA-1 is known to increase the solubility of copper salts in organic solvents and was often used as a phase-transfer catalyst.[74]



R = 2-Cl, 3-Cl.

The use of *trans*-*N*,*N*′-dimethyl-1,2-cyclohexanediamine (**22**) as the ligand enabled the amidation of aryl iodides, bromides and chlorides in high yields (Table 2). CuI proved to be the substance of choice as the copper source. Other copper(I) or copper(II) compounds [CuCl, CuSCN, Cu_2O, $Cu(acac)_2$] and copper powder afforded the reaction products in lower yields. The choice of the base is even more important. Thus with strong bases, namely, potassium hexamethyldisilazide (KHDMS) or NaOBu^t, the reaction proceeded in a yield of 1% or 10%, respectively. However, slow addition of KHDMS to the reaction mixture resulted in virtually complete conversion of the starting haloarene. This pointed to the coincidence of rates of amide deprotonation and amidation. Accumulation of excess of deprotonated amide resulted in the formation of non-reactive copper amide complexes (for details, see Section IV.7). The pK_{HA} value of the base should also be lower than

Table 2. Reaction of chloroarenes with carboxamides.[75, 76]



R^1	Amide	T/°C	Yield (%)
Me	$BzNH_2$	110	93
Me		130	95
MeO		130	51
CO_2Me		130	62

the pK_{HA} value of the amide. Thus, K_2CO_3 and K_3PO_4 were the most suitable bases for carrying out this reaction, being thermodynamically strong in aprotic solvents and poorly soluble in non-polar organic solvents.

5. N-Arylation of NH-heterocycles

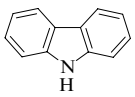
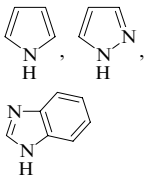
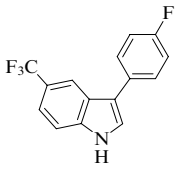
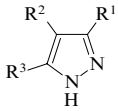
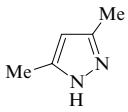
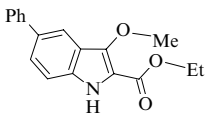
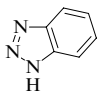
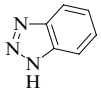
Copper, its oxides and salts catalyzed N-arylation of NH-heterocycles (pyrrole, pyrazole, imidazole, their derivatives and benzo analogues). The catalysis occurred both in the presence and in the absence of ligands.

a. Ligandless catalysis

On heating to 170–250 °C in the presence of copper powder and K_2CO_3, carbazole reacted with substituted chloronitrobenzenes. The yields of the N-arylation products were low and dropped to 10% in the absence of catalyst; only with chlorodinitrobenzene, the yield did not change and amounted to 50% (Table 3).[77]

The Ullmann condensation with activated chloroarenes was effectively catalyzed by copper(I) oxide covered with copper nanoparticles. The latter was prepared by heating

Table 3. Reaction of chloroarenes and chlorohetarenes (ArCl) with NH-heterocycles.

Ar	Heterocycle	Catalyst	Base	Solvent	T/°C	t/h	Yield (%)	Ref.
2-$O_2NC_6H_4$, 2-NO_2-4-MeC_6H_3, 2-NO_2-4-ClC_6H_3, 2,4-$(NO_2)_2C_6H_3$, 2-NO_2-4-CNC_6H_3		Cu	K_2CO_3	–	170–250	3–12	15–50	77
4-$O_2NC_6H_4$, 4-AcC_6H_4, 4-$F_3CC_6H_4$, 4-$CHOC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 2-Py, 4-Py		5 mol % Cu_2O/Cu	Cs_2CO_3	DMSO	150	18	63–97	78
4-$F_3CC_6H_4$, 2-Py		10 mol % Cu_2O	KOH	DMSO	130	24	88–89	79
3,6-Dialkylpyrazin-2-yl (Alk = Me, Bu^t), 3,5-diphenylpyrazin-2-yl		5 mol % CuI	K_2CO_3	DMA [a]	reflux	12	37–72	80
4-Py		CuBr	K_2CO_3	NMP [b]	"	18	31	81
5-Nitropyridin-2-yl, 6-methylpyridin-2-yl	 ($R^1 = R^3 = H$: $R^2 = H, NO_2$; $R^1 = R^3 = Ph$, $R^2 = NO_2$)	CuO	K_2CO_3	pyridine	"	24	20–58	82
6-Methoxy-4-methyl-quinolin-2-yl		CuO	K_2CO_3	"	"	28	6	83
2-NO_2-4-ClC_6H_3		CuO	K_2CO_3	"	"	24	45	84
Anthraquinon-1-yl		$Cu(OAc)_2$	KOAc	$PhNO_2$	"	–	–	85
See [c]		$Cu(OAc)_2$	KOAc	$PhNO_2$	"	–	–	86

[a] DMA is *N*,*N*-dimethylacetamide; [b] NMP is *N*-methyl-2-pyrrolidone; [c] ArCl is 6,11-dichloronaphthacene-5,12-dione.

copper acetylacetonate in oleylamine and afforded no arylation products only with unsubstituted chlorobenzene and its analogues with electron-donating substituents. The reaction proceeded in DMSO at 150 °C in the presence of caesium carbonate as the base.[78] The high catalytic activity was explained by the large surface and also by the possible coordination of oleylamine to copper nanoparticles. This assumption was confirmed by the fact that conventional copper(I) oxide was slightly less active in amination of chloroarenes containing strong electron-withdrawing substituents. The reaction was carried out in the DMSO – KOH system at 130 °C for 24 h. For iodo- and bromoarenes, the product yield was 85% – 92%.

Copper(I) and copper (II) salts can also be used as the catalysts (see Table 3).

The high activity was manifested by the heterogeneous catalyst CuFAP prepared from the *in situ* formed fluoroapatite by ion exchange with Cu^{II}.

$$Ca(NO_3)_2 \cdot 4H_2O + (NH_4)_2HPO_4 + NH_4F \longrightarrow$$
$$\longrightarrow Ca_{10}(PO_4)_6F_2 \xrightarrow{Cu(OAc)_2} CuFAP$$

In the presence of CuFAP, chloro- and fluoroarenes reacted with pyrrole, pyrazole, benzimidazole, piperidine. The reaction proceeded in DMF (K_2CO_3, 120 °C) with activated haloarenes for 1 – 10 h in yields of 88% – 95% and also with deactivated haloarenes for 1 – 36 h in yields of 55% – 85%.[87]

b. Catalysis in the presence of ligands

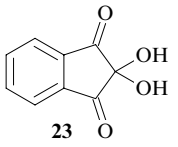
The reaction of 2-chloropyridine with pyrazole and benzimidazole was catalyzed by copper powder in the presence of 1,1′-binaphthyl-2,2′-diol (BINOL) in DMSO at 125 °C with caesium carbonate as the base. The yield of the arylation product was 85% – 88%.[88]

The role of bidentate *O*,*O*-ligands could also be played by compounds **23** – **28** of which the Cu_2O – **23** system was the most effective (Table 4);[89] KOH proved to be the base of choice. In this case, low yields were obtained with potassium and caesium carbonates and potassium phosphate. The role of a solvent was of no lesser importance. Thus virtually no reaction occurred upon the exchange of DMSO for the less polar toluene.

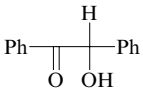
In the presence of copper(I) bromide, 2-aminopyrimidine-4,6-diol (**29**) and Bu^n_4NF, different imidazoles underwent N-arylation in moderate yields. High yields (up to 100%) were obtained in the reactions of azoles with 2-chloropyrimidine. The transformation took place at high temperature and under solvent-free conditions.[90]

With the system CuI – **30**, milder conditions can be employed.[91] *N*-[(*S*)-Pyrrolidin-2-ylmethyl]imidazole derivative **30** is sufficiently stable and can be obtained from inexpensive reagents in high yields. The arylation should be carried out in polar solvents in the presence of caesium carbonate with the ratio CuI : **30** ~ 1 : 2.

In the series of ligands **31** – **35**, the highest arylation yields were obtained in the presence of caesium carbonate, copper acetate and hippuric acid (**35**) as the ligand. Other bases were not effective in this case.[92]



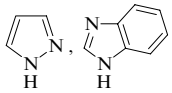
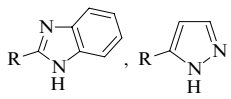
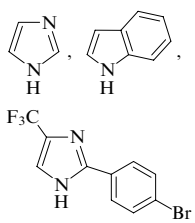
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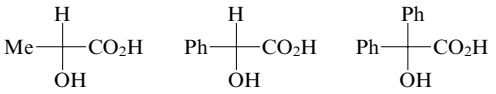
24

$AcCO_2K$
25

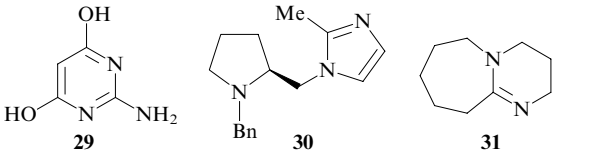
Table 4. Reaction of chloroarenes and chlorohetarenes (ArCl) with NH-heterocycles in the presence of different ligands.

Ar	Heterocycles	Catalyst	Ligand	Base	Solvent	*T*/°C	*t*/h	Yield (%)	Ref.
2-Py		1 mmol Cu	BINOL [a]	Cs_2CO_3	DMSO	125	48	85 – 88	88
Ph, 4-MeC_6H_4, 4-$F_3CC_6H_4$, 2-Py		0.1 mmol Cu_2O	**23**	KOH	DMSO	130 – 150	24 – 48	46 – 91	89
Ph, 4-$O_2NC_6H_4$, 2-Py, pyrimidin-2-yl	 (R = H, Me)	10 mol % CuBr	**29**	Bu^n_4NF	–	145 – 150	24	40 – 100	90
4-$O_2NC_6H_4$, 4-NCC_6H_4, 3-Py		5 mol % CuI	**30**	Cs_2CO_3	DMF	110	24	92 – 97	91
Ph, 4-$O_2NC_6H_4$		20 mol % $Cu(OAc)_2 \cdot H_2O$	**35**	Cs_2CO_3	DMF	140	20	55 – 87	92

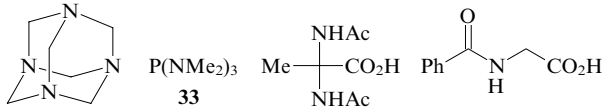
[a] BINOL is 1,1′-binaphthyl-2,2′-diol.



26 **27** **28**

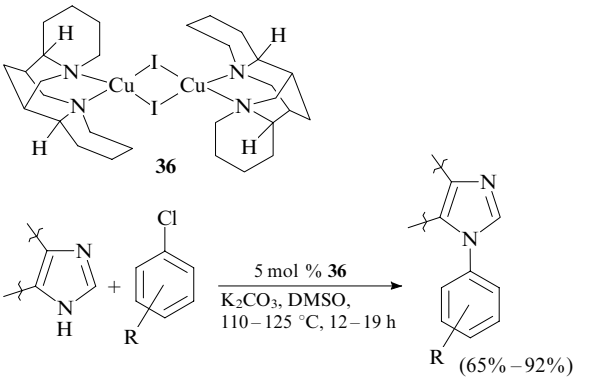


29 **30** **31**



32 **33** **34** **35**

The reaction of activated chloroarenes with imidazole and benzimidazole proceeded with high efficiency when catalyzed by the complex $\{Cu_2I_2[(-)\text{-sparteine}]_2\}$ (**36**).[93] At the same time, non-activated chlorobenzene (R = H) afforded < 10% of the arylation product even after 24 h.

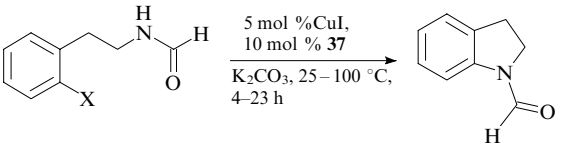


36

R = 4-NO_2, 2-NO_2, 4-CN, 2-CN, 4-CF_3, 4-Ac, 4-CHO.

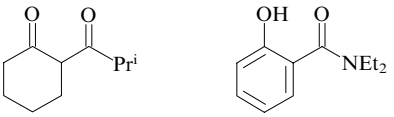
6. Intramolecular amination and amidation reactions in the synthesis of heterocycles

Intramolecular amination and amidation in the presence of copper-containing catalysts can also be used in the synthesis of heterocycles and their derivatives. Such reactions proceed more readily than intermolecular reactions, *e.g.*, for bromides they occur at room temperature.[75]



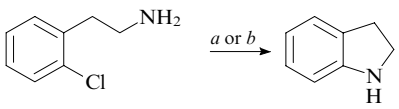
X = Cl (88%), Br (100%); **37** = $MeNH(CH_2)_2NHMe$.

Diketone **38** and amide **39** can serve as the ligands.[94,95]



38 **39**

In the latter case, the reaction should be carried out either for 48 h at 50 °C or for 14 h at higher temperature (100 °C).



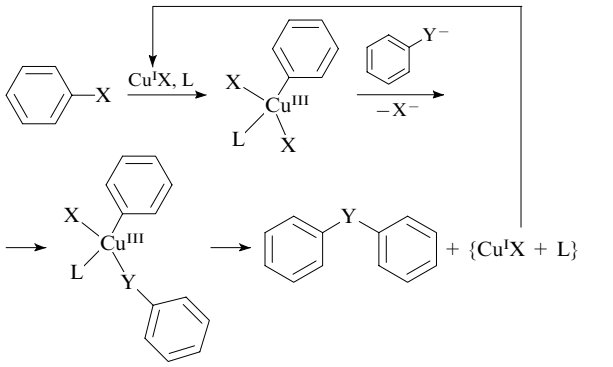
(*a*) 5 mol % CuI, 20 mol % **38**, Cs_2CO_3, DMF, 60 °C, 10 h, yield 86%;
(*b*) 5 mol % CuOAc, 20 mol % **39**, K_3PO_4, DMF, 50–100 °C, 14–48 h, yield 78%.

7. Mechanisms of amination, amidation and N-arylation

The mechanism of copper-catalyzed formation of a C–N bond is not reliably elucidated so far.[59]

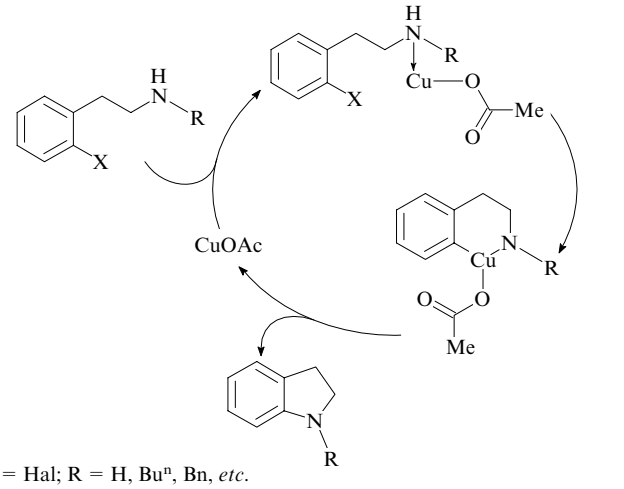
Generally, the catalytic cycle of the Ullmann intra- and intermolecular reactions is described by Schemes 5 and 6. Presumably, the reaction proceeds *via* Cu^I and Cu^{III} intermediates involved in the oxidative addition, transmetallation and reductive elimination steps.

Scheme 5



X = Cl, Br, I; Y = NH, O.

Scheme 6



X = Hal; R = H, Bu^n, Bn, *etc.*

In contrast to palladium and nickel, copper can take part in the single-electron transfer by the radical mechanism (*e.g.*, in the Sandmeyer reaction).[96]

$$RX + Cu^I \longrightarrow R^{\bullet} + X^- + Cu^{II},$$

$$R^{\bullet} + Nu^- \xrightarrow[-e^-]{} RNu.$$

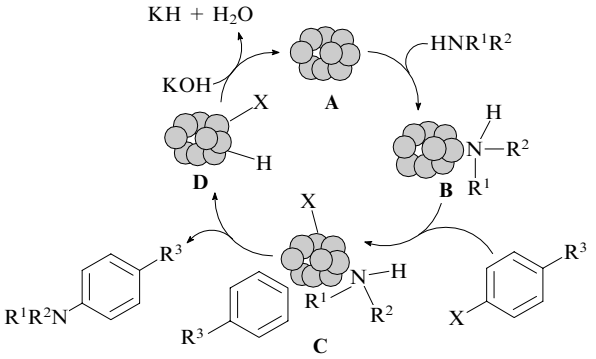
Another peculiarity of copper is its ability to easily acquire oxidation states from 0 to +3, whereas palladium and nickel are for the most part characterized by oxidation states 0 and +2.

Moreover, copper compounds including its complexes are poorly soluble in many organic solvents. It is quite difficult to assess the catalyst fraction involved in transformations. It is due to insufficient solubility that these reactions were initially carried out at high temperatures in the presence of stoichiometric amounts of copper or its salts. The use of either ligands capable of stabilizing Cu^{III} intermediates or readily soluble copper complexes made it possible to carry out amination under substantially milder conditions.

Let us consider in more detail several specific examples of the catalytic cycle of the Ullmann reaction.

With CuO nanoparticles (**A**) as the catalyst (Scheme 7), the amination also involves the oxidative addition and reductive elimination steps. The stabilization of CuO by dimethyl sulfoxide and the amine results in an active cluster **B**. The oxidative addition of chloroarene to the latter produced intermediate **C** with the positive charge shared among CuO nanoparticles on the surface of the cluster. The intermediate **C** transforms by reductive elimination providing the formation of a new C–N bond. The heterogeneous catalyst is recyclable without loss of activity.[66]

Scheme 7



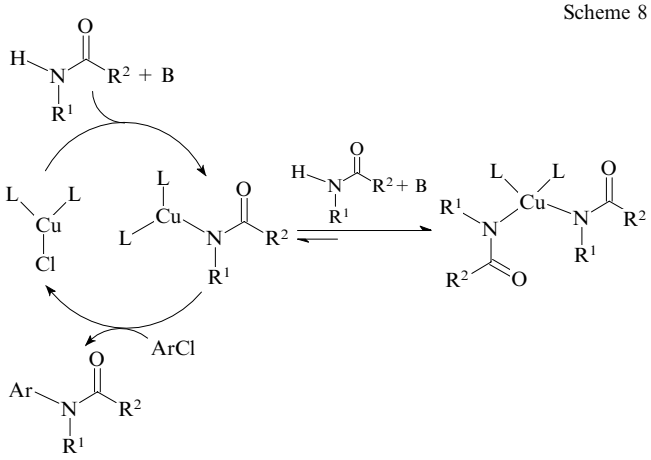
— CuO; R^1, R^2 = H, Alk, Ar; R^3 = H, NO_2, MeO; X = I, Br, Cl.

Scheme 8 presents the catalytic cycle of amidation of chloroarenes in the presence of copper complexes and diamines (for example, amine **22**). Note that in the presence of an excess of the deprotonated amide, unreactive cuprate complexes are presumably formed.[75]

On the whole, the mechanism of reactions of chloroarenes with NH-heterocycles catalyzed by the copper complex with ligand **29**, conforms to the general scheme of N-arylation (Scheme 9). The formation of a chelate complex of Cu^I with diol **29** (**A**) results in an increase in the reactivity of Cu^I thus favouring the oxidative addition of the chloroarene to chelate **A** and simultaneously stabilizing intermediate **B**. In the presence of a base, the latter reacts with imidazole to form intermediate **C** and the reductive elimination of the latter affords the final N-arylation product.[90]

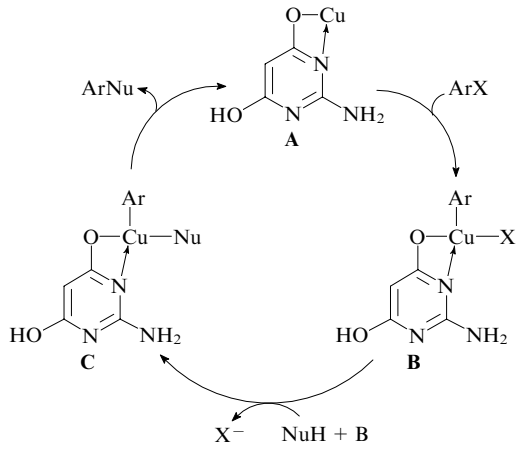
Scheme 10 shows the tentative catalytic cycle that involves the heterogeneous catalyst CuFAP. In the arylation of imidazole (HetNH), its blue complex with copper-containing catalyst **A** was formed in the first step. The subsequent reaction with chlorobenzaldehyde afforded the final *N*-arylimidazole and converted the catalyst into either its Cu^{II} form **B** under ambient conditions or its Cu^I form in nitrogen atmosphere.[87]

Scheme 8



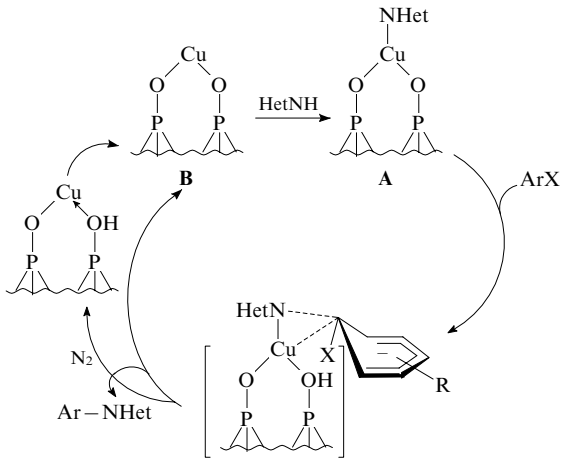
L is a diamine, B is a base; for Ar, R^1, R^2, see Table 2.

Scheme 9



Ar = 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$, 2-Py, 2-thienyl, *etc.*; X = Br, Cl; NuH is imidazole.

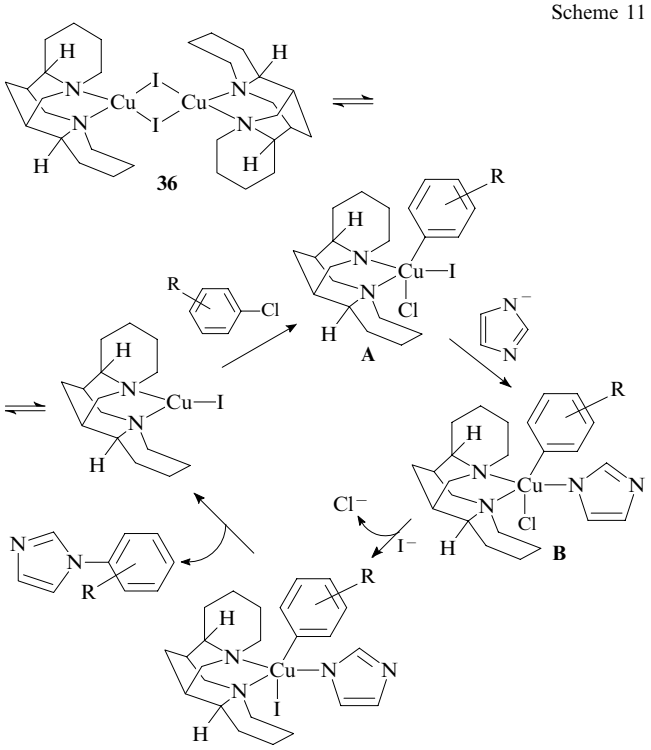
Scheme 10



The oxidative addition of a chloroarene to Cu^I–(−)-sparteine complex (**36**) produced Cu^{III} intermediate **A** (Scheme 11). Nucleophilic substitution of the imidazole anion for I^- in intermediate **A** led to complex **B**.[93] This assumptions was substantiated by the results of calculations which explained the high reactivity of complex **36**

towards aryl chlorides: the key role is played by the differences in the geometry and the binding energy of Cu^{III} intermediates **A** and **B**.

Scheme 11



R = 2-NO_2, 4-NO_2, 2-CN, 4-CN, 4-CF_3, 4-Ac, 4-CHO.

V. Conclusion

According to the material presented in this review, different nature and, hence, different activities of catalysts based on transition metals impose specific requirements to the structure of chloroarenes that undergo amination reactions. It cannot be denied that more detailed studies are required for sound conclusions, the more so that the amination mechanism is not completely clear. At the same time, based on the currently available information, certain conclusions can be drawn.

Thus the high activity and good solubility of nickel-containing catalysts allowed the amination to be carried out for substrates deactivated by electron-donating substituents. The use of copper compounds and complexes often required more drastic conditions or the presence of electron-withdrawing groups in the substrate. The known iron-based catalysts allowed so far only the reactions of N-arylation of heterocycles with haloarenes to be carried out.

On the whole, despite the permanent progress in the field of metal complex catalysis, the examples of amination, amidation and N-arylation of heterocycles in the presence of transition metals are indeed scarce. Chloro derivatives of aromatic compounds that exhibit the lower reactivities as compared with bromo- and iodoarenes are the most easily accessible and cheap substrates, which stimulates the search for new more active catalytic systems, *i.e.*, synthesis of new ligands and complexes and variation of the reaction conditions.

For a long time, attention of scientists was focused on reactions catalyzed by palladium compounds. However, it is already obvious that palladium is far from being the only candidate for the leadership among the metals that find their application in the syntheses based on cross-coupling reactions carried out in both laboratories and industry.

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