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Review

Copper in cross-coupling reactions The post-Ullmann chemistry

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Contents

Abstract

In the last decade, a number of methods using various copper complexes and salts to carry out cross-coupling reactions leading to the formation of C—heteroatom (C—N, C—O, C—S, C—P, C—Se), C—C, and C—metal bonds have been proposed. These methods aim at overcoming the deficiencies of conventional copper-assisted substitution methods (Ullmann chemistry) due to dramatic softening of reaction conditions,

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extension of scope towards unactivated substrates and new types of nucleophiles, and increasing tolerance to sensitive functionality. On the other hand, the scope and selectivity of copper-assisted methods are often complimentary to the parallel palladium-catalyzed cross-coupling methods. Both the new features and drawbacks of the new family of synthetic protocols are discussed.

Keywords: Copper; Catalysis; Cross-coupling; Ullmann reaction

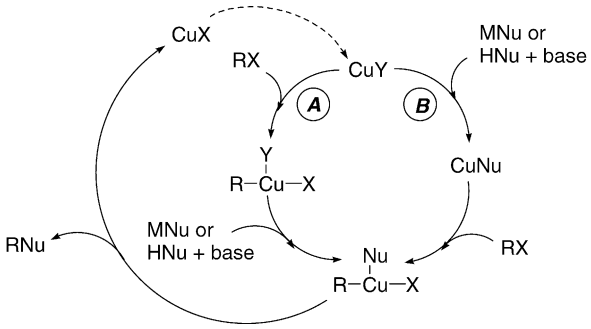
1. Introduction

The *cross-coupling* is so closely associated today with palladium catalysis, that both terms are often regarded as inseparable parts of an idiom. Tremendous development of palladium-catalyzed methods of C–C and C–heteroatom bond formation during the last three decades is the basis of such a way of thinking. A certain effort is required to realize that the cross-coupling chemistry is actually much older (cf. e.g. [1]), and that another metal, copper, has been the ancestor of palladium in this domain. Classical Ullmann chemistry along with closely related methods have been known for a full century and served well for C–N, C–S, C–O and some other bond formation reactions [2]. C–C bond formation has been excellently serviced by organocuprate chemistry [3–6]. However, after the discovery of palladium catalyzed cross-coupling reactions copper has been suffering an increasing degree of neglect. A critical point was the discovery and fast development of palladium-catalyzed amination, which conquered the last stronghold of copper – the synthesis of arylamines in which the classical Ullmann and Goldberg reactions had kept an exclusive and unshakable position. Since then the only use for old chemistry could be to become a target of criticism in describing new advanced procedures, even though palladium chemistry itself has a number of inborn deficiencies (not only high cost, but also essential restrictions in scope). However, it turned out that copper is not too easy to get rid of. The last years witness a steady increase of interest in copper assisted cross-coupling chemistry with dozens of new effective procedures emerging in all areas. Is this a renaissance? In order to answer this question, it is useful first to collect together what already has been discovered. In the recent years, a number of excellent reviews on various aspects of copper-assisted reactions appeared, two of them published when this manuscript was being prepared [2,7–9], covering various aspects of this chemistry. None of them, however, considers copper-catalyzed *cross-coupling* as a special subject, thus not permitting us to draw a parallel to palladium catalyzed cross-coupling chemistry.

Cross-coupling is a generic term used to denote a σ-bond metathesis reaction between a nucleophilic and electrophilic reagent, and thus can be regarded as a generalization of nucleophilic substitution. Many such reactions take place only in the presence of catalyst (Eq. (1)).

$$\overset{(E)}{RX} + \overset{(N)}{MNu}\ (\text{or HNu + base}) \xrightarrow{\text{cat.}} RNu \qquad (1)$$

The role of catalyst is generally believed to take part in successive oxidative addition, transmetallation, and reductive elimination reactions.



Scheme 1.

The overall evidence gained so far tells us that copper can take part in cross-coupling chemistry in a way strikingly similar to palladium. Moreover, copper is apparently more versatile and productive than its closest neighbor in the Periodic System, nickel, a lighter and much less capable brother of palladium.

The most important difference of copper is an easy accessibility of four oxidation states from 0 to +3, while palladium has at its disposal only two stable oxidation states—0 and +2. There are indeed +1, +3 and +4 oxidation states for palladium [10], but these are either extremely rare or play no unambiguously identifiable role in cross-coupling reactions. Most likely, the cross-coupling catalytic cycle with copper is serviced by +1/+3 oxidation states.

A rough picture of the possible catalytic cycle driven by Cu is given in Scheme 1, omitting all details, such as ancillary ligands, etc. This is not a mechanism, but rather an approximate presentation of what may happen, based on analogies and general considerations, and not on actual mechanistic studies. Therefore, any refinements of this scheme, which may occasionally be met in the literature, are mostly speculative. This is not an indication of the poor state of copper catalysis, as the current status of understanding of mechanism of palladium-catalyzed cross-coupling is not much better, that apparently not being a serious handicap in the avalanche development of Pd-catalyzed methods. Unlike Pd-driven cross-coupling in which an oxidative addition step is believed to precede the transmetallation, the ordering of oxidative addition and transmetallation steps in the copper cycle is unknown, so either of two possibilities can take place (ways A or B).

The other notable difference between copper and palladium is the accessibility of odd-electron states in copper, implying that copper can take part in redox single-electron transfer processes, and thus an alternative free-radical mechanism should be taken into consideration. Such mechanisms (Eq. (2)) are believed to be prevalent in Sandmeyer reactions

[11–14] occurring when arenediazonium salts are used as electrophilic reagents in Cu(I) assisted nucleophilic substitution, but could not be ruled out with other leaving groups.

$$\begin{aligned} &RX + Cu(I) \rightarrow R^{\bullet} + X^{-} + Cu(II) \\ &R^{\bullet} + Nu^{-} \xrightarrow{-e^{-}} RNu \end{aligned} \quad (2)$$

In this review, we have undertaken to collect the cases which can be classified as copper-driven cross-coupling reactions, which implies: (a) the net reaction complies to the formal cross-coupling scheme (Eq. (1)) and (b) copper in any form is an essential reagent not involved in the stoichiometric equation, thus it can be regarded as a catalyst (or pre-catalyst).

The latter condition is essential. On the one hand, it rejects all chemistry where copper reagents are preformed and then explicitly brought into the reaction with electrophilic coupling partner, such as in organocuprate chemistry, or the reactions where copper reagents are required by stoichiometry, e.g. as oxidants. On the other hand, it permits us not to fix on such a formal parameter, as the amount of copper reagent used to perform a given reaction, whether it is catalytic, equivalent, or even in excess. Indeed, in a lot of cases, copper reagents are very poorly soluble in the reaction medium, so we cannot be certain which part of reagent put into the reaction vessel is actually working, so that the need to add more copper salt can be caused by just the need to make the reaction run at a decent rate. As Cu is much cheaper than Pd, almost nobody bothers to optimize the amount of copper, as soon as the required yield of target products is achieved, while in the case of palladium-driven reaction the cost of palladium makes the optimization of catalytic efficiency a vital task. For possible industrial applications the cost of copper is not negligible, so that a reaction cannot have an industrial perspective without being made catalytic on copper [15].

The formal mechanism (Scheme 1) reveals that Cu(I) is regenerated at the product forming reductive elimination step as a compound CuX, which may bear different ligands than the compound CuY which entered the catalytic cycle. Therefore, the regeneration, in this case, means the regeneration of oxidation state, and not exactly of the form used to initiate the cycle. This form may or may not be reactive, it may or may not undergo ligand exchange to form the active species that enters the second turn of the catalytic cycle. If this form is not reactive, the cycle is disrupted, and we cannot regard the reaction as catalytic, though the chemistry involved in a single turn is exactly the same as it would be if the reaction were catalytic, capable of two or more turns. In fact, this means that the factors effecting the deactivation of copper catalysts remain poorly understood.

These considerations show that in the cross-coupling reaction Cu(I) effectively serves as the catalyst, while the turnover number (TON), a criterion of catalysis, is in many cases equal to or even higher than unity. We believe that the TON criterion is not critical for the current state of copper assisted cross-coupling chemistry, and shall not distinguish the reactions by this parameter. It is most likely that any of the reactions to be discussed can be made catalytic if proper attention is paid to the optimization of reaction conditions, proper choice of copper compounds and ligands, investigation of chemistry which accounts for the activation and deactivation of copper catalysts.

We have not taken into consideration a large group of methods which employ Cu(II) to perform the reaction between two nucleophilic reagents, the organometallic RM (the derivatives of B, Sn, Si, Bi, Zn, Al, etc.), and N- or O-nucleophiles (Eq. (3)), which have been discussed already in the reviews [2,7,8], particularly in [9] specially devoted to this type of chemistry:

$$RM + M'Nu + CuX_2 \rightarrow RNu + MX + M'X + Cu(0) \quad (3)$$

These reactions require a stoichiometric participation of Cu(II), formally as a two-electron oxidant. In some cases such reactions can be made catalytic through the addition of an extra oxidant which recycles Cu(II). Very similar chemistry exists with Pd(II) as a stoichiometric reagent or as a catalytic reagent in the presence of a stoichiometric oxidant, e.g. the Fujiwara reaction [16], the arylation of olefins by organomercuric, organotin or organolead compounds discovered by Heck in parallel with his famous reaction [17] (later made catalytic on palladium by the use of stoichiometric Cu(II) oxidant, cf. [18–23]). Anyway, this is an essentially different chemistry, which should not be confused with "true" cross-coupling. It should only be noted, that current views on the mechanism of these reactions involve the formation of the same Cu(III) intermediate (Eq. (4)) as in the catalytic cycle given above, so that, with respect to product formation steps, the underlying chemistry is similar to "true" cross-coupling. The complexity of catalytic cycles however should effectively mask any common features, even if any existed.

$$CuX_2 \xrightarrow{RM} \left[RCuX \xrightarrow[-e^{-}]{Nu^{-}} R{-}\overset{\displaystyle Nu}{\underset{|}{Cu}}{-}X \right] \longrightarrow RNu \quad (4)$$

The scope of this review is further limited by choosing only those methods, which can be regarded as improvements over the classical Ullmann chemistry ([24,25], review [26] and references cited therein). The latter has no exact definitions, but conventionally it refers to all aromatic nucleophilic substitution reactions in the presence of copper or copper salts, which take place under drastic conditions (prolonged heating in the absence of solvent or in high-boiling solvents at temperatures above 150–200 °C). The other common feature of "old" Ullmann chemistry is the preference for haloarenes with electron-withdrawing substituents. The review, in contrast, focuses on "new" methods that overcome the drawbacks of Ullmann chemistry by: (a) softening the conditions, e.g. by decreasing reaction temperatures, choosing simpler and more convenient solvents; (b) substantially widening the scope, e.g. to electron-rich and/or sterically hindered substrates, alkenyl halides, substrates with sensitive functionality prohibited from drastic handling, etc. These improvements are so essential, that the methods implementing

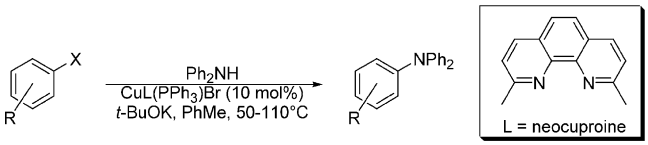
them should not be considered as an extensive improvement of Ullmann methods. This should be considered a new, post-Ullmann chemistry, probably rivaling the closely related palladium catalyzed cross-coupling methods.

2. C–N bonds

2.1. Arylation of aromatic amines

Copper-promoted arylation of aromatic amines, originally diarylamines, has been known for a century as the classical Ullmann reaction [24]. The reaction requires harsh prolonged heating at 200 °C or higher, in the presence of simple Cu(I) or Cu(II) salts or oxides, or Cu bronze, etc., in the presence of base in polar high-boiling solvents. In spite of modest yields and severe limitations imposed on both amine and aryl halide reagents, this reaction has until recently been regarded as the only viable approach to triarylamines, compounds with rich and versatile practical potential. The discovery of Pd-catalyzed amination (the Buchwald–Hartwig reaction) has been a major breakthrough in the chemistry of amines, opening access to huge numbers of previously inaccessible compounds. A new interest in much cheaper and more practical copper-catalyzed chemistry has been brought about by the observations that appropriate ligands can modulate the reactivity of catalyst, and thus enable us to achieve more effective and more versatile catalytic systems.

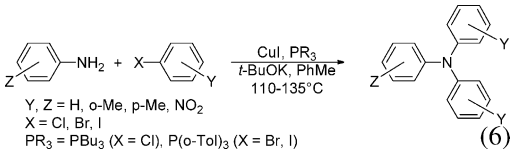
Unlike the classical Ullmann method, the reactions with copper complexes are best performed in non-polar solvents, such as toluene, at reflux or lower temperatures. Bidentate ligands, including aliphatic diamines, 1,10-phenanthroline and its derivatives, 2,2′-bipyridine, 8-hydroxyquinoline, bidentate phosphines, of which bis-diphenylphosphinopropane (dppp) is the best can all be used with comparable results to achieve the arylation of anilines by aryl iodides in the system CuI/L, *t*-BuOK, PhMe, 115 °C [27]. The readily available ligand 1,10-phenanthroline is the most practical choice for arylation by aryl iodides. Both monoarylation and diarylation can be successfully achieved in the system CuCl/phen, KOH, PhMe. The system shows good catalytic activity even at 50 °C, though for practical reasons higher temperatures, up to reflux, are recommended [28]. Aminoacids with secondary amino-group, e.g. *N*-methylglycine or proline are also effective as ligands, and allow for the use of weaker bases such as K_2CO_3 in DMSO, though the scope of this method with respect to aromatic amines has not been investigated in detail [29]. Alternatively, the soluble complexes of Cu(I) with 1,10-phenanthroline, neocuproine, or 2,2′-bipyridine CuL(PPh_3)Br, can be employed. Such complexes are convenient due to good stability towards air and moisture, and solubility in common organic solvents (dichloromethane, chloroform, toluene, benzene, NMP, DMF, and DMSO). The activity of such complexes is apparently higher, allowing for the use not only of aryl iodides, but also of aryl bromides to perform arylation of diphenylamine in the presence of *t*-BuOK base. Moreover, yields up to 50% can be obtained with chlorobenzene as arylating agent. *t*-BuONa and Cs_2CO_3 are less effective, while weaker bases are altogether ineffective (Eq. (5)) [30].



(5)

So far, copper-catalyzed cross-coupling chemistry has been restricted to iodo and bromo derivatives, while chloro-derivatives have been considered as unlikely targets for this chemistry with only a few exclusions discussed below in the appropriate sections. This situation vividly reminds us about what had been going on in palladium catalysis some 5–6 years ago. Since then a number of highly effective and practically useful catalytic systems have been proposed for virtually all sorts of cross-coupling reactions involving chloroarenes. It should thus be expected that we should not wait too long for the development of potent copper-based catalytic systems, tailored to chlorides. The first steps in this direction have already appeared.

It turns out that some monodentate phosphines, such as tri-*o*-tolylphosp hine P(*o*-tol)$_3$ and tri-*n*-butylphosphine PBu_3 are highly effective ligands for the arylation of anilines by aryl halides from iodides to chlorides, in sharp contrast to PPh_3, which is practically ineffective even for aryl iodides. While P(*o*-tol)$_3$ is one of the most widely used and valuable ligands in Pd-catalyzed cross-coupling reactions, PBu_3, as other simple trialkyl phosphines, is not useful for common palladium-catalyzed cross-coupling chemistry, which shows that any parallels with palladium catalysis should be drawn with due care in order not to discard valuable approaches. In this copper-catalyzed protocol PBu_3 turned out to be the ligand of choice for the most challenging aryl chloride substrates (Eq. (6)) [31].



(6)

The influence of potentially coordinating *ortho*-substituents on the rates and yields of Ullmann reaction was known long before the introduction of ligand-assisted copper catalysis. This effect can be interpreted as an intramolecular ligand assistance. Thus, *o*-halobenzoic acids (even chlorobenzoic acid) has been shown to undergo amination by anilines to give *N*-arylanthranilic acids under rather mild conditions, such as heating in aqueous or DMF solutions, in the presence of pyridine, or sonication at r.t. [32–36]. The reaction of *o*-chlorobenzoic acid and α-aminopyridine under such conditions leads to 11*H*-pyrido[2,1-*b*]quinazolin-11-one system [37,38].

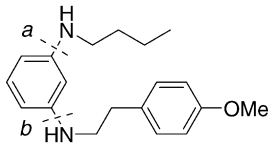


Fig. 1. Conditions: (a) CuI (100 mol%), CsOAc, DMSO, r.t. (b) CuI (100 mol%), CsOAc, DMSO, 90%.

2.2. Arylation of aliphatic amines

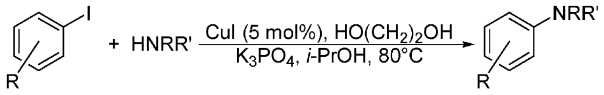
While the conventional Ullmann reaction is poorly suited to the arylation of aliphatic amines, new ligand-assisted methods immediately brought forward several enticing protocols for this purpose. However, non-catalytic ligand-free Ullmann chemistry should not be altogether discarded, as is evident, e.g. from a recent observation that CsOAc used as base enables one to perform the arylation of primary aliphatic amines by aryl iodides under very mild conditions [39]. An interesting feature of this method is the possibility to perform one-pot stepwise substitution of iodine atoms in *meta* or *para*-diiodobenzene as, e.g. in Fig. 1.

Besides primary aliphatic amines, this method is applicable to pyrrolidine, aniline, indole, as well as some amides, though the reported examples are too few to elucidate the actual scope. *Ortho*-substituted iodoarenes however do not react, which unfavorably distinguishes this method from the ligand-assisted protocols described below.

Intramolecular assistance by neighboring coordinating groups can be observed, though the examples are quite rare. In earlier studies it has been noted that copper(I) triflate in aqueous acetone in the presence of ammonia induced room temperature ammonolysis of methyl *o*-iodobenzoate [40]. The amination of 1-(*o*-bromophenyl)isoquinolines is performed in high yield under mild conditions (Fig. 2) [41].

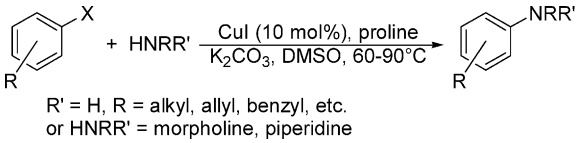
Ligand-assisted methods enable us to dramatically extend the capabilities of the method. Currently, the major restriction for Cu-catalyzed reactions is low reactivity of secondary non-cyclic amines, most likely due to steric reasons, so the scope of amines usually includes primary aliphatic and saturated secondary heterocycles, such as piperidine, piperazine, pyrrolidine, morpholine, etc. Such bases as K_2CO_3, K_3PO_4, Cs_2CO_3 are usually chosen in various solvents, both non-polar and polar.

Simple vicinal diols showed high efficiency for the arylation of aliphatic amines by aryl iodides. Ethylene glycol was earlier shown to facilitate the ammonolysis of aryl and heteroaryl iodides and bromides, which can be successfully performed in the presence of as low as 0.5 mol% Cu_2O at temperatures as low as 80 °C [42]. Further it has been shown that vicinal glycols can be used as ligands. The most efficient ligand of this series again turned out to be trivial ethylene glycol, used in two-fold excess over amine (Eq. (7)) [43]. Arylation of aliphatic amines is achieved in hydroxylic solvent in the presence of K_3PO_4 as base. CuI is the best copper source, though other Cu(I) and Cu(II) compounds are reactive. The chelating effect of glycols is likely to be a critical factor, as both monoatomic alcohols, and remote diols are ineffective.



The method has been applied for the preparation of 6-aminoimidazo[1,2-*a*]pyridines from the respective iodo-derivative [44].

The other ligands suitable for the arylation of aliphatic amines by aryl iodides are aminoacids. In order to exclude competitive self-arylation of ligand, aminoacids with secondary amino-group should be chosen, e.g. *N*-methylglycine or proline, while *N*,*N*-dimethylaminoacids are less efficient as ligands (Eq. (8)) [29].



(8)

Arylation of secondary cyclic amines and primary aliphatic amines can be alternatively run in *N*,*N*-dimethylaminoethanol as solvent under mild conditions, in which case only one atom of halogen is selectively substituted in dihalobenzenes (Fig. 3) [45].

While in the classical Ullmann reaction the differences of reactivity between aryl bromides and iodides is not great [46], in ligand-assisted methods different systems are to be chosen for bromo and iodoarenes. For the former glycols are inefficient, and *ortho*-substituted phenols should be used instead. Good results can be achieved with such readily phenols as 2,6-dimethylphenol or 2-phenylphenol (a cheap commercial fungicide), if the reaction is carried out either in excess amine or toluene at 100 °C [43]. Further optimization has led to the use of amides of salicylic acid as ligands, which enables us to avoid the excess of amine under very mild conditions. The scope of this method is very wide, aryl bromides can contain free OH, NH_2, COMe groups, *ortho*-substituents. Heteroaryl bromides can be aminated as well. The reaction is chemoselective, as shown in the examples of compounds, which can thus be synthesized (Fig. 4) [47].

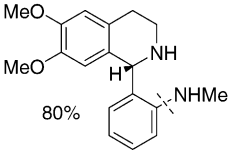


Fig. 2. Conditions: Cu/CuCl, $MeNH_2$, 70 °C.

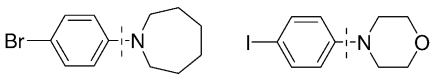


Fig. 3. Conditions: CuI (10 mol%), K_3PO_4, $Me_2NCH_2CH_2OH$, 55–60 °C.

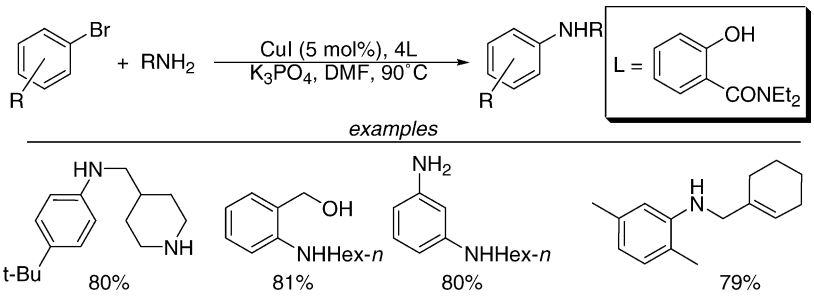
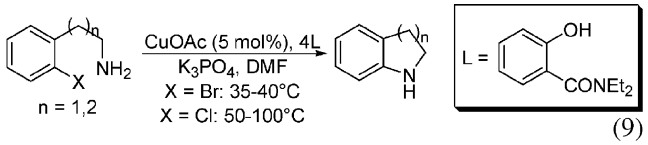


Fig. 4. Copper catalyzed arylation of aliphatic amines in the presence of salicylamides.

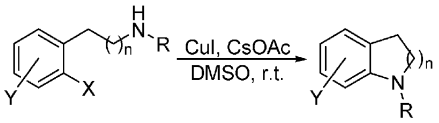
Additionally, the reaction can be run under solvent-free conditions, which is essential for environmentally friendly applications.

Intramolecular arylation can be successful even with chlorides (X = Br or Cl) (Eq. (9)) [47]:



(9)

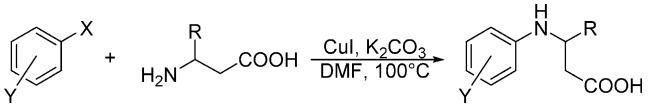
A different protocol for intramolecular reaction under very mild conditions has been proposed. The preference for cyclization is so high that halogen atoms present in the substrate in other positions are retained in the product (Eq. (10)) [48].



(10)

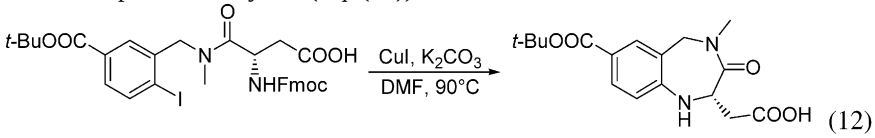
2.3. Arylation of functionally substituted alkylamines

As aminoalcohols or aminoacids can serve as ligands for Cu, the arylation of such compounds can be done in the absence of extra ligands. Both alpha [49], and beta-aminoacids [50] can be arylated in moderate to good yields by aryl iodides or bromides (Eq. (11)). The reaction is run under mild conditions in DMF. The addition of small amounts of water has been found to be beneficial in some cases [49,51]. The simplest aminoacid, glycine is not reactive under these conditions.



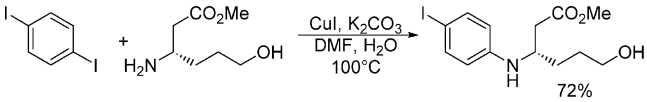
R = Alk, Ar; Y = H, o- or p-Cl, NO_2, NH_2, OMe, Me, etc. (11)

Intramolecular versions of this reaction may be used to obtain complex heterocycles (Eq. (12)) [50]



(12)

An interesting feature of this method is the possibility to substitute only one halogen of two iodines or bromine atoms in *p*-dihalobenzene. In cross-coupling chemistry the task to accomplish partial substitution usually requires the use of different halogens. This approach has been successfully utilized during the synthesis of complex natural compounds (Eq. (13)) [51]



(13)

Arylation of aspartic acid by aryl iodides or bromides is best performed if in situ generated tetrabutylammonium salt of this aminoacid is used (Fig. 5) [52,53].

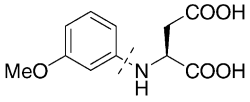
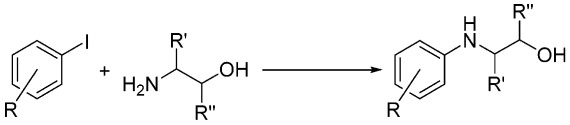


Fig. 5. Conditions: CuI, Bu_4NOH, MeCN, 80 °C.

Arylation of aminoalcohols by aryl iodides faces the problem of N/O-selectivity. Two protocols are used: (a) CuI (2.5 mol%), NaOH, DMSO–water (2:1) or *i*-PrOH as solvent, 90 °C; apparently aminoalcohol here serves as ligand and (b) CuI (2.5%), ethyleneglycol (stoichiometric), K_3PO_4, *i*-PrOH, 75 °C (Eq. (14)). The first protocol gives better N/O-selectivity, but is less tolerant to functional groups due to the use of stronger base [54]



(14)

Method A. CuI (2.5 mol%), NaOH, DMSO-H_2O or *i*-PrOH, 90°C
Method B. CuI (2.5 mol%), K_3PO_4, $HO(CH_2)_2OH$, *i*-PrOH, 75°C

The choice of non-hydroxylic nitrile solvent allows one to completely invert the selectivity and perform arylation at hydroxy-group (cf. section C–O bonds).

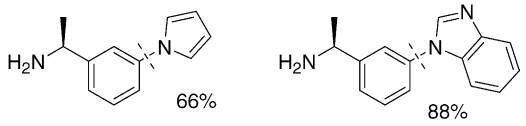


Fig. 6. Conditions: CuI (10 mol%), K_2CO_3, NMP, μW, 2 h.

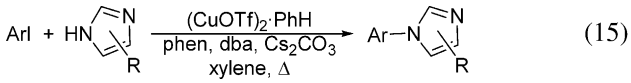
2.4. Arylation of unsaturated heterocycles

Conventional Ullmann methods are applicable to imidazole and other azoles, but suffer from usual drawbacks of this chemistry. Limited improvements can be achieved through microwave heating successfully achieved for a wide selection of azoles including pyrrole, pyrazole, imidazole and their benzo-derivatives and aryl bromide containing free amino-group (Fig. 6) [55].

The use of aryl bromides capable of intramolecular assistance, e.g. *o*-bromobenzoic acid also allows for dramatic softening of the conditions of Ullmann arylation, e.g. to use the system CuI (10 mol%), K_2CO_3, DMF, 100 °C [56].

However, a major breakthrough in this area came only with the introduction of ligand-assisted methods. A number of effective protocols has been put forward for the arylation of aromatic heterocycles containing pyrrole-type nitrogen during recent years.

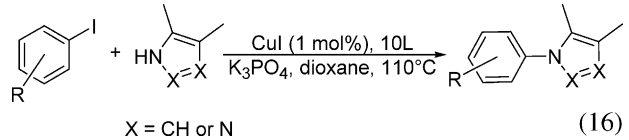
One of the first systems proposed was based on a rare organic-solvents-soluble salt of Cu(I), the triflate, which is available as benzene solvate $(CuOTf)_2{\cdot}PhH$, additionally requiring dibenzylideneacetone (dba) and 1,10-phenanthroline. This system enabled us to perform the arylation of imidazoles in non-polar solvents in the presence of Cs_2CO_3 as base (Eq. (15)) [57].



(15)

The same system can be applied for other aminations as well, e.g. for the reaction of 5-iodouracyl with various amines [58]. Though highly effective, this system is too sophisticated due to many components and expensive copper salt requiring special handling precautions. Quite soon it was demonstrated by many researchers that ligand assisted arylation procedures can generally be catalyzed by much simpler and cheaper derivatives of copper, and that solubility of Cu catalyst precursor is not a critical parameter.

Commercial racemic *trans*-cyclohexyldiamine (CyDA, cf. Fig. 7 for diamine ligands, and abbreviation used throughout this review) is an effective ligand for copper-catalyzed arylation of mono- or dinitrogen azoles (including pyrroles, pyrazoles, indoles, indazoles, benzimidazoles, carbazoles, etc.) by aryl iodides (Eq. (16)) [59].



(16)

Further optimization of this system towards the arylation of indoles revealed that dimethylated amines DMEDA and

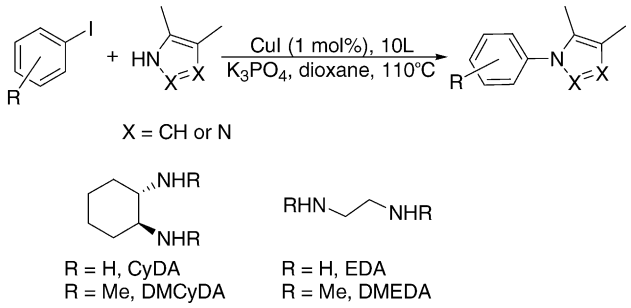


Fig. 7. *Vic*-diamine ligands.

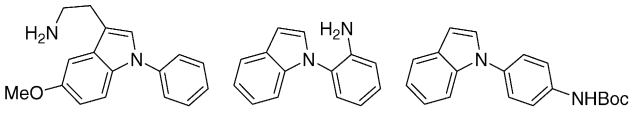
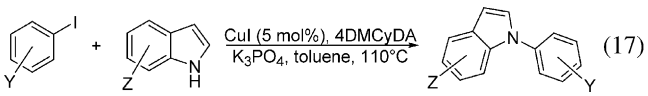


Fig. 8. Examples of *N*-arylindoles synthesized by method shown in Eq. (17).

DMCyDA are more suitable, as no self-arylation of ligand occurs, which is one of main reasons for lower yields obtained if cheaper diamines EDA or CyDA are used. Practically all Cu sources (e.g. Cu bronze, $Cu(OAc)_2$, $CuCl_2$, $Cu(OMe)_2$) can be used, though CuI is a superior pre-catalyst giving consistently better yields of arylation products, particularly in challenging cases (e.g. *ortho*-substituted bromoarenes). The choice of solvent is also not a critical parameter, with toluene being selected only due to favorable combination of many parameters (Eq. (17)) [60]



(17)

Both indole and haloarene can contain amino or amido groups, e.g. the compounds in Fig. 8 can be synthesized in high yields [60].

Arylation of resin-supported indoles by aryl iodides or bromides in a similar system (CuI, CyDA, *t*-BuOK, dioxane) has been described [61].

The aminoacid with a secondary amine nitrogen, proline, is the other effective ligand for the arylation of azoles (pyrrole, indole, carbazole, pyrazole, imidazole) by iodoarenes under mild conditions (CuI (10 mol%), proline, K_2CO_3, DMSO, 75–80 °C) [62].

Alkynylation of indoles and pyrroles can be carried out in the presence of copper(II) sulfate and 1,10-phenanthroline (Fig. 9) [63].

Iodonium salts, very reactive electrophiles, can be used for the arylation of azoles (as well as other nitrogen nucle-

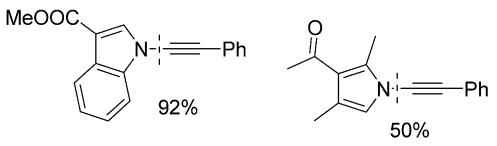


Fig. 9. Conditions: $CuSO_4{\cdot}5H_2O$ (10 mol%), phen, K_3PO_4, toluene, 70–80 °C.

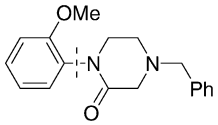
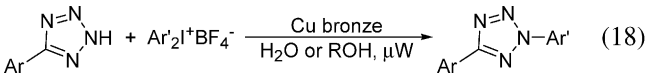


Fig. 10. Conditions: CuI (2.5 mol%), K_2CO_3, NMP (2 eq), μW, 1 h.

ophiles including aliphatic amines, anilines, and amides) in the presence of CuI or Cu(acac)$_2$ (5–10 mol%), K_2CO_3 as base under mild conditions in toluene or CH_2Cl_2 [64], or reflux in DMF [65,66]. Selective arylation of very weak nucleophile, tetrazole, can be achieved using diaryliodonium salts and microwave irradiation in aqueous or alcoholic solvents (Eq. (18)) [67].



(18)

2.5. Arylation of amides

The copper-promoted arylation of amides (in a rigorous sense, acetanilides) is the classical Goldberg reaction [25,68]. The drawbacks of the conventional Goldberg method are similar to those of the Ullmann reaction, i.e. the extreme harshness of conditions (heating to reflux of haloarene in the presence of anhydrous K_2CO_3 and Cu bronze or CuI), severe restrictions on both aryl halide and amide (acetanilides bearing no fragile or reactive additional functionality) (cf. [69] and refs. therein). In spite of such limitations, the Goldberg reaction has been occasionally used for rather complex tasks, e.g. stepwise assembly of oligo-anilines [70]. Some improvement can be achieved, e.g. through the application of microwave heating, which effectively furnishes very high temperatures of the reaction mixture within dramatically shortened time. The reaction can be performed in the absence of solvent, with a small amount of NMP added to furnish the absorption of microwave energy, with impressively high catalytic efficiency (Fig. 10) [71], or in NMP solution (Fig. 11) [72].

The recent development of ligand-assisted methods allowed for softening of the conditions of the reaction, which immediately greatly widened its scope and possibilities. As amides to a certain extent resemble azoles in nucleophilicity and NH-acidity, the arylation methods of these two classes are generally the same or very similar.

Vicinal diamines, particularly ethylenediamine (EDA) [73] and *rac-trans*-cyclohexanediamine (CyDA), as well as their *N*,*N*-dimethyl derivatives (DMEDA and DMCyDA) are excellent ligands for this purpose, the latter pair usually more suitable for more challenging tasks. The system

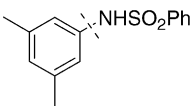


Fig. 11. Conditions: CuI (10 mol%), K_2CO_3, NMP, μW, 2 h.

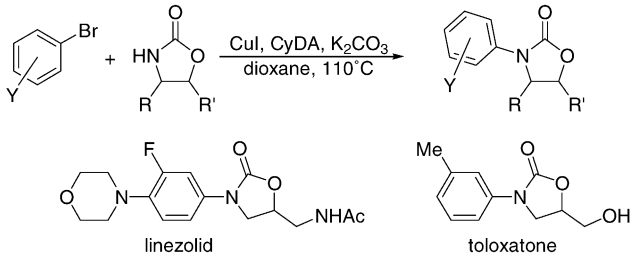
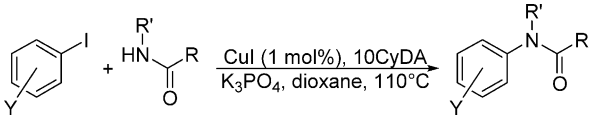


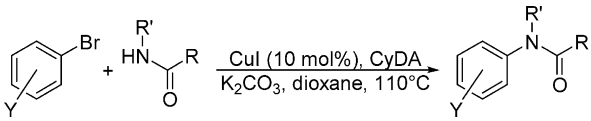
Fig. 12. Arylation of cyclic carbamates by aryl bromides.

CuI (1 mol%), diamine ligand (10 mol%) is highly effective for the arylation of amides by aryl iodides with (K_3PO_4 or Cs_2CO_3 as base, in various solvents (toluene, dioxane, THF, DMF) at reflux or lower temperatures (Eq. (19)). The use of stronger bases inhibits the reaction because the amidate formed binds to copper and inhibits the catalytic process [59,74]



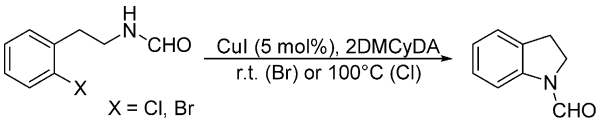
(19)

The arylation is highly chemoselective, gives no disubstitution for N-unsubstituted amides, and allows for selective attack at amide N to be performed in the presence of a free aniline NH_2 group. As most other ligand-assisted methods described in this paper, this method is not sensitive to donor or *ortho*-groups in aryl iodides. The reactions are run under mild conditions, and with more reactive substrates the temperature can be brought down, even to r.t. Aryl bromides are equally reactive though up to 10% CuI may be required, and K_2CO_3 used as base (Eq. (20)) [59,74].



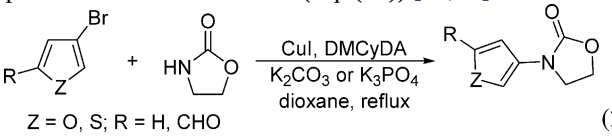
(20)

Even aryl chlorides, including electron-rich *p*-chlorotoluene and *p*-chloroanisole, can be used for the arylation of amides if DMCyDA is used as ligand, in excess ArCl as solvent [59]. An intramolecular version gives a convenient approach to heterocycles (Eq. (21)) [74]



(21)

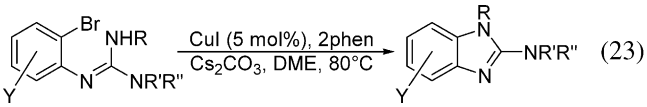
The method has been applied to bromofurans, bromothiophenes and bromothiazoles (Eq. (22)) [75,76]



(22)

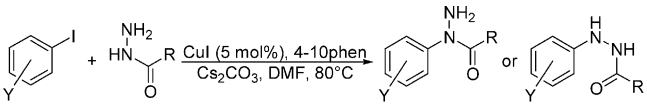
Arylation of cyclic carbamates (oxazolinones) by aryl bromides has been used to develop a short route to potent antibacterial agents linezolid and toloxatone (Fig. 12) [77].

Besides amides, arylguanidines can be used in intramolecular arylation to yield the derivatives of 2-aminobenzimidazole (Eq. (23)). Here, as in many other cases copper-catalyzed reaction turns out to be more selective than a similar Pd-catalyzed route [78]



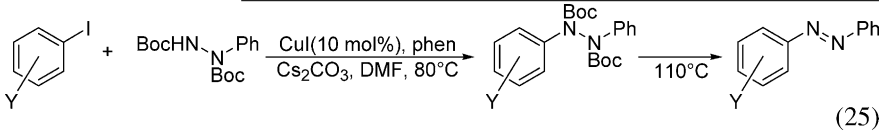
(23)

The arylation of hydrazides (*N*-bochydrazine or benzoylhydrazine) by aryl iodides requires the system (CuI 1–5%, phen 10–20%, Cs_2CO_3, DMF, 80 °C), a marked improvement over ligandless system [79]. The substitution is directed at amide nitrogen for *para*- or *meta*-substituted ArI, while *ortho*-substituted ArI showed a complete reversal of regioselectivity to give mostly symmetrically substituted hydrazines (Eq. (24)) [80].



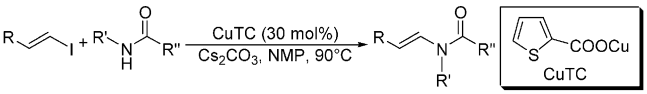
(24)

Arylation of Boc-protected phenylhydrazine is performed under the same conditions, but at higher temperatures hydrazines are converted by the same system to azobenzenes (Eq. (25)) [81]



(25)

Ligand-assisted copper catalysis is also applicable for the alkenylation of amides, and a number of useful protocols has been published. Liebeskind's catalyst copper(I) thiophene-2-carboxylate (CuTC), works best in polar solvents (NMP, DMSO) in the presence of Cs_2CO_3 or Rb_2CO_3 under strictly anhydrous and air-free conditions (Eq. (26)) [82,83]



(26)

Due to mild conditions the configuration of double bond, which in such compounds is very prone to isomerization in the presence of bases, is not affected, which is illustrated by successful synthesis of both (*E*) and (*Z*)-isomers of unsaturated amides. For complex syntheses a fine adjustment of catalytic system may be required. The yields of products can be improved by addition of chelating ligands, such as DMCyDA, 1,10-phenanthroline, dba, dipivaloylmethane, etc. (e.g. Figs. 13 and 14) [83–86], use of Rb_2CO_3 in place of Cs_2CO_3 is sometimes remarkably of critical importance (Fig. 15) [87].

A similar system employing CyDA as ligand has been used for the synthesis of a complex natural compound. Noteworthy is that mild conditions and high selectivity of this method make it well suited for use in the last steps of a long synthesis with the compound burdened by numerous fragile functionalities (Fig. 16) [88].

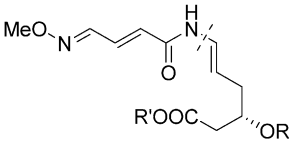


Fig. 13. Conditions: CuTC, phen, dba, Cs_2CO_3, DMAc, 65 °C.

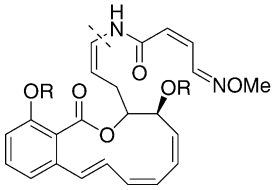


Fig. 14. Conditions: CuTC, DMEDA, K_2CO_3, 50 °C.

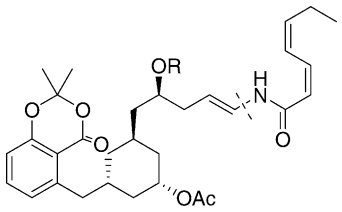


Fig. 15. Conditions: CuTC, Rb_2CO_3, DMA, 90 °C.

In a recent report, it was shown that for some complex cases a system CuI or $Cu(MeCN)_4PF_6$ with 3,4,7,8-tetramethyl-1,10-phenanthroline ligand can give serious advantages in the alkenylation of amides (Fig. 17) [89].

Alternatively, the alkenylation of amides and carbamates by alkenyl bromides can be achieved in a simpler system CuI, K_2CO_3, toluene, 110 °C in the presence of diamines, of which the best is DMEDA (while DMCyDA is inferior,

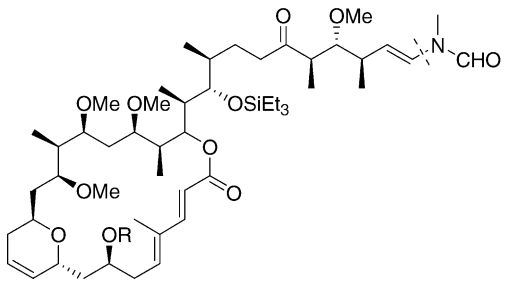


Fig. 16. Conditions: CuI, CyDA, K_3PO_4, dioxane, 60 °C.

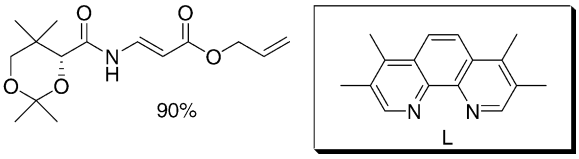
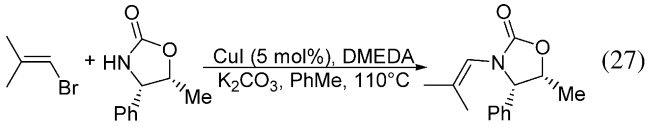


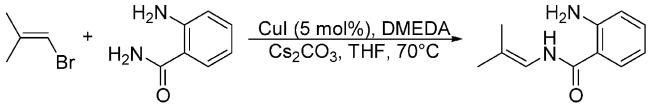
Fig. 17. Conditions: $Cu(MeCN)_4PF_6$, 2L, Rb_2CO_3, DMA, 45 °C.

and other amines are practically ineffective) [90], e.g. in Eq. (27)



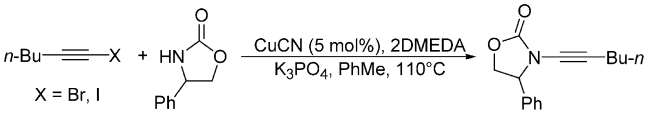
(27)

Alkenyl iodides can be used under even milder conditions (r.t., 70 °C) [90], e.g. in Eq. (28)



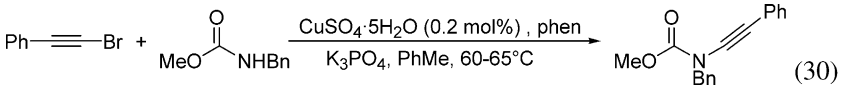
(28)

A similar protocol can be used for the alkynylation of amides by iodo- or bromoacetylenes in the presence of either CuI or CuCN [91]. Bromoacetylenes are more selective, as no homocoupling product is formed (Eq. (29)).



(29)

An alternative approach uses copper (II) sulfate and 1,10-phenanthroline. This system is more effective as it requires only 0.2 mol% of the catalyst (Eq. (30)). In this method, the use of DMEDA ligand results in poor yields [63].



(30)

A ligand free system is useful for the alkynylation of carbamates by bromoacetylenes taking place under very mild conditions but requiring a stoichiometric amount of copper iodide and strong base, potassium hexamethyldisilazide (py, r.t., 20 h) [92].

2.6. Comparison with Pd-catalyzed C–N cross-coupling reactions

A serious drawback of the palladium catalyzed amination protocol has been the necessity to use strong bases, such as *t*-BuONa, which essentially limited the overall tolerance of the method to base-insensitive functional groups. In this respect Cu-catalyzed procedures requiring milder bases are an improvement, particularly for base sensitive reagents. However, with the recent introduction of special bulky ligands allowing for Pd-catalyzed amination reactions to be carried out

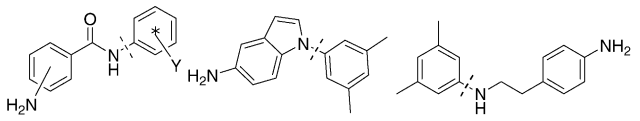


Fig. 18. Examples of compounds formed by cross-coupling using the system CuI, DMEDA or CyDA, K_2CO_3, dioxane, 100–110 °C.

under much milder conditions and employ soft bases, such as K_2CO_3, etc., there has been considerable expansion of the synthetic potential of the Buchwald–Hartwig method. Generally, in synthetic applications Pd-catalyzed amination so far has no rivals. However, the potential of new ligand-assisted copper catalyzed reactions is considerable. The advantages of copper-catalyzed amination chemistry, besides the cost of metal and ligands, and the overall cost of synthetic procedure (Pd catalyzed amination reactions, particularly those involving high-performance ligands, require a higher level of experimental work, place more stringent requirements to the quality of solvents and reagents, benefit from the use of special expensive techniques, such as inert atmosphere glovebox, etc.) are associated with a different reactivity profile. Though the scope of Pd-catalyzed amination reaction is currently wider, copper catalysts permit us to address different synthetic targets. In general, copper catalysts show a better tolerance to reactive functionality, which is vulnerable to palladium catalysts. Pd and Cu catalyzed reactions may show a complementary chemoselectivity. While Pd catalysis preferentially attacks aromatic amino-group, copper catalyzed reactions have a richer choice of targets including amide, azole, or aliphatic amine nitrogens, which makes it possible to perform selective reactions with unprotected compounds bearing several different centers, as on the examples below (Fig. 18, bonds marked by dotted line are formed in the systems CuI, DMEDA or CyDA, K_2CO_3, dioxane, 100–110 °C) [93].

Copper catalyzed reactions are generally more selective giving exclusively monosubstitution in those cases when disubstitution is possible. Thus, a selective monoarylation of diamines, e.g. of the ligand CyDA itself by aryl bromides can be achieved in the system CuI, CyDA, K_3PO_4 [59].

3. C–P bonds

There are only a few reports describing the application of copper derivatives for the formation of C–P bonds, however clearly showing a formidable potential of copper in this chemistry. C–P bonds can be obtained in cross-coupling in both possible ways—using phosphorus reagent either as electrophile or nucleophile, and copper reagents have been utilized with success in both approaches.

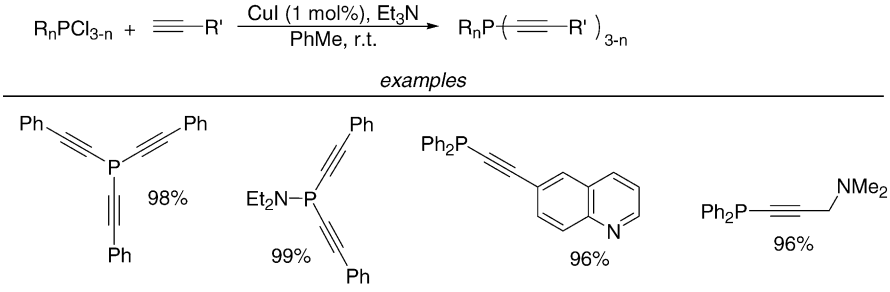
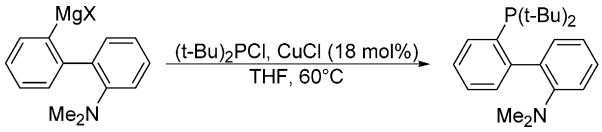


Fig. 19. Copper catalyzed synthesis of alkynylphosphines.

The positive influence of CuCl on the yields of tertiary phosphines in the reaction of aryllithium compounds with bis(dichlorophosphino)ethane has been reported [94]. The reactions of aryl iodides or alkenyl bromides with the stoichiometric amounts of CuCl complex of triethylphosphite at high temperature give the respective phosphonates [95,96]. The addition of catalytic amounts of CuCl is essential in a high-performance procedure for the synthesis of bulky Buchwald's phosphine ligands (Eq. (31)) [97]



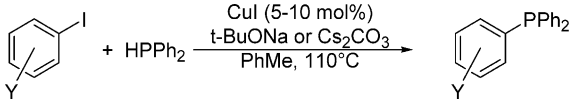
(31)

Alkynylphosphines can be conveniently prepared from terminal acetylenes and chlorophosphines in a highly effective procedure using only 1 mol% CuI or CuBr as catalysts, under mild conditions in toluene solution at r.t. in near to quantitative yields (Fig. 19) [98].

Using a phosphorus reagent as a nucleophile, the copper-catalyzed arylation of phosphites in the presence of CuI was the first reaction of this type to be described as early as 1983 [99].

Several copper(I) catalyzed methods for cross-coupling of secondary phosphines with aryl halides have been proposed. As phosphines themselves are good ligands for copper, no extra ligand may be required.

Thus, triarylphosphines can be obtained by cross-coupling of aryl iodides with Ph_2PH in the presence of CuI, and K_2CO_3, K_3PO_4 or Cs_2CO_3 as bases (Eq. (32)). The addition of extra ligands or the use of copper complexes with phosphine or 1,10-phenanthroline ligands does not improve the yield [100]



(32)

Similar results were obtained in another study [101]. However, an excess of secondary phosphine was shown to be necessary in order to effect full conversion, thus leading to an essential complication during the isolation of reaction product, as the separation of two phosphines is required. The addition of ligand, of which the best was found to be DMEDA, gives a more general protocol, in which both reagents are

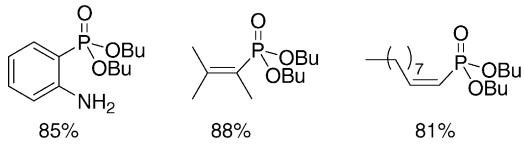
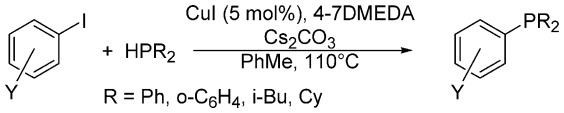


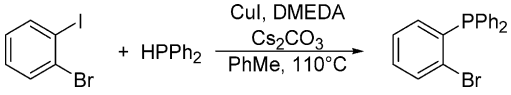
Fig. 20. Examples of phosphonates formed by copper catalyzed cross-coupling with dibutylphosphite (Eq. (35)).

used in stoichiometric amounts to give very high yields of pure target triarylphosphines (Eq. (33)). Free amino groups in aryl iodide do not interfere with the reaction. The reaction is applicable also to secondary dialkylphosphines, though very bulky molecules, such as *t*-Bu_2PH give poor yields [101].



(33)

Chemoselective displacement of iodine takes place with iodobromoarenes (Eq. (34)).



(34)

The same protocol is effective for cross-coupling of aryl iodides, alkenyl bromides and iodides with dialkylphosphites (Eq. (35)):

$$RX + HP(O)(OBu)_2 \xrightarrow[\text{PhMe, 110 °C}]{\text{CuI (5 mol\%), 4L, } Cs_2CO_3} RP(O)(OBu)_2 \quad (35)$$

The reaction is chemo and stereospecific, and not sensitive to steric hindrance, as geminally substituted alkenylhalides give high yields of the respective phosphonates, e.g. in the examples in Fig. 20.

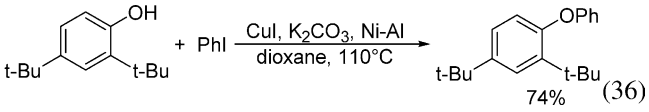
The arylation of phosphites was earlier shown to take place in the presence of CuI in the absence of extra ligands [99].

4. C–O bonds

Several ligand-free protocols have been described for the arylation of phenols by aryl iodides or bromides under relatively mild conditions resembling those typically used for ligand-assisted processes Iodo and bromoarenes containing

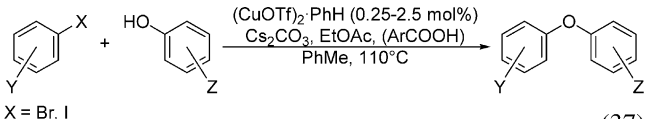
electron-withdrawing substituents can react with phenols under mild conditions in the absence of copper, if common means of nucleophilic activation are used, e.g. the reaction is carried out in polar aprotic solvents (DMSO, NMP, etc.), in the presence of bases with cesium or tetraalkylammonium counterions, under microwave heating, etc. [102–104]. Thus, the potential of any catalyzed method should be revealed for unactivated haloarenes.

Several published protocols do not use any specially added ligands, but perform the reaction under mild conditions. It is likely that phenols themselves may serve as ligands in such reactions. Ligand effects of phenols on copper-catalyzed arylation of alkylamines are well known (cf. section Arylation of aliphatic amines). In some approaches, the application of soluble copper derivatives, such as $CuBr{\cdot}Me_2S$ or methylcopper [105,106], facilitates the reaction and allows for effective ether synthesis from non-activated aryl iodide and phenols under moderate temperatures. Various additives are usually required to facilitate such reactions. Thus, the addition of catalytic amounts of Raney Ni–Al alloy has been reported to enable a facile arylation of phenols by aryl iodides or bromides in the system CuI (10 mol%), K_2CO_3, Ni–Al alloy, dioxane, 110 °C. Sterically hindered phenols give the arylation products in good yields [107], as e.g. in Eq. (36)



(36)

Even aryl chlorides are reactive under such conditions, though the yields are modest. The role of Raney's alloy in this reaction is not clear, and a slightly different combination of conditions affords similar results in the absence of this additive. Thus, the arylation of phenols by aryl bromides or iodides can be accomplished in the presence of catalytic amounts (0.5–2.5%) of copper salts (CuCl, CuBr, CuI, $CuBr_2$, and $CuSO_4$ gave similar results, while $(CuOTf)_2{\cdot}PhH$ was the best due to enhanced solubility) and Cs_2CO_3 as base in TolH as solvent. Cs base and non-polar solvent are essential for success of this protocol. Among phenols some simple ones (phenol itself, *p*-cresol, *p*-chlorophenol) gave poor results, possibly due to poor solubility of respective copper phenolates, or just because such phenols are not effective ligands, similarly to that noted in arylation of amines, where only *o*-substituted phenols were highly effective ligands. The addition of equimolar amounts of carboxylic acids, such as naphthoic acid, improved the yields (Eq. (37)) [108].



(37)

This method has been successfully tested in a number of published syntheses of diaryl ethers, particularly in medicinal chemistry, e.g. of the analogues of antibacterial agent triclosan [109], new anticancer agents [110].

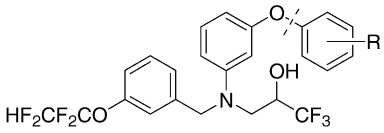


Fig. 21. Conditions: $(CuOTf)_2{\cdot}PhH$, Cs_2CO_3, naphthoic acid, PhMe, EtOAc, 100 °C, 48–96 h.

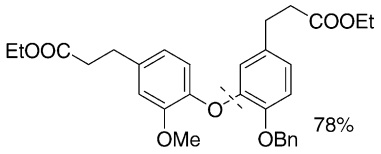


Fig. 22. Conditions: $(CuOTf)_2{\cdot}PhMe$, Cs_2CO_3, py, 110 °C.

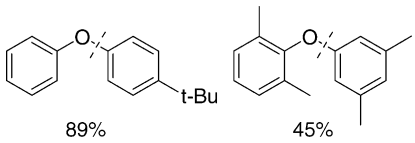


Fig. 23. Conditions: CuI (10 mol%), Cs_2CO_3, NMP, microwave heating.

This method has been successfully employed for generating a library of compounds containing diaryl ether fragment for pharmaceutical screening [111]. The reactions were accomplished using a parallel synthesis setup, and were found to give consistently good yields for all arylating agents except those bearing electron-withdrawing substituents, most likely due to competitive non-catalyzed S_NAr reaction, which can be less selective to involve other nucleophilic centers in this multifunctional molecule (Fig. 21).

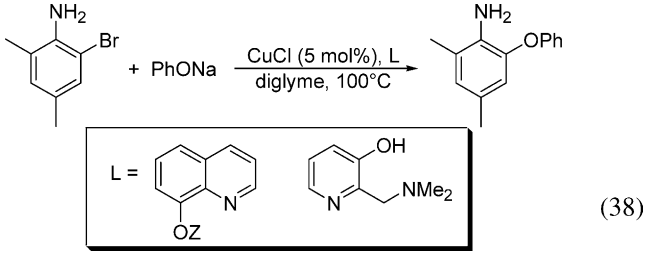
In another published example, the successful coupling between aryl bromide and phenol was achieved without the addition of carboxylic acid, in pyridine solvent (Fig. 22) [112].

Microwave heating allows for the arylation of phenols by unactivated aryl iodides and bromides to be performed in the absence of any additives. As is usual in microwave driven processes, negative effects of overheating are compensated by shorter reaction times (system CuI (10 mol%), Cs_2CO_3, NMP, microwave heating 2 h) [113]. Reasonable yields can be achieved even for *o*,*o*-disubstituted phenols (Fig. 23).

Attempts to design recyclable catalytic systems for copper-catalyzed arylation have met with only partial success. Arylation of phenols by aryl iodides can be done in ionic liquids media (1-*n*-butyl-3-methyl-imidazolium salts: bmiI, bmiBr, or bmiCl, bmi[BF_4]) catalyzed by CuI (or CuBr, CuCl) at 110–130 °C and K_2CO_3 or *t*-BuONa as base [114,115]. Aryl bromides are unreactive. Ionic liquid phase with copper catalyst can be reused only three times after extraction of reaction products [114].

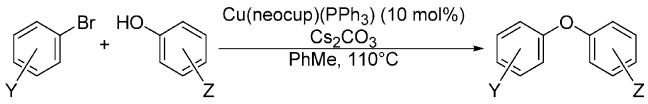
A number of ligand-assisted methods appeared recently. A wide screening of 96 various pyridine and quinoline derivatives as ligands for phenoxylation of model substrate by phenoxide has been undertaken [116]. Very high sensitivity to ligand was observed, with by far the best being 8-hydroxyquinoline and its esters that give close to quantita-

tive yields of phenoxy derivative. Among pyridine derivatives, the only good candidate was 2-dimethylaminomethyl-3-hydroxypyridine, though it gave lower yields (Eq. (38)). This study is rather illustrative for this chemistry, as definitely no rational reasoning can be applied for the intentional design of ligands. Probably chelation is desirable, but which other factors define the best choice remains unknown. Questionable also is the choice of model substrate for this study, as *ortho*-amino group can lend assistance for substitution.



(38)

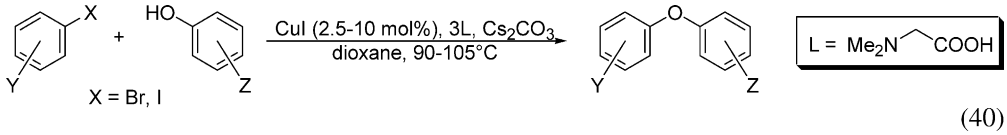
In other protocols, phenols were chosen as nucleophiles in the presence of base, usually, as in ligand-free methods, Cs_2CO_3. Phenanthroline and neocuproine complexes $CuL(PPh_3)Br$ are effective in the arylation of phenols by aryl bromides [30] in toluene (Eq. (39)).



(39)

In NMP solvent, the complex $Cu(PPh_3)_3Br$ is effective in the absence of 1,10-phenanthrolines for electron-rich bromoarenes, the best yields being obtained with 20 mol% catalyst in the presence of Cs_2CO_3 in NMP at 70–100 °C [102].

An alternative ligand for this reaction is *N*,*N*-dimethylglycine allowing for the arylation of phenols by both aryl iodides and bromides to be performed under roughly the same conditions (Eq. (40)) [117].

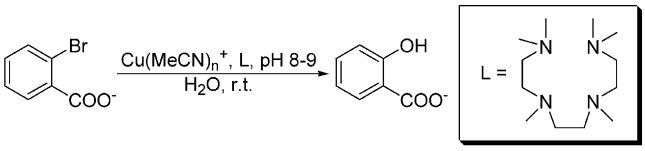


(40)

In both methods, a wide range of substituents in phenol and aryl halide including electron-withdrawing and electron-donor groups in *o*-, *m*- and *p*-positions is tolerated.

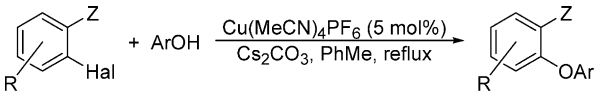
The third protocol for the same purpose requires dipivaloylmethane as ligand, and is achieved in the system CuCl (50 mol%), L (10–25 mol%), Cs_2CO_3, NMP, 130 °C [118]. The reactivity and selectivity profile of this method is roughly the same as the previous two. High loading of the catalyst and relatively high temperature make this method apparently inferior to the above approaches. An interesting feature of this method is the use of ligand in less amounts than Cu salt.

The helper ligand can be attached to the substrate. The influence of *ortho*-carboxylic group in *o*-halobenzoic acids is well documented [119,120]. The formation of soluble Cu(I) carboxylates or Cu(I)-arene π-complexes has been noted [121,122]. As a result, a mild hydrolysis of *o*-bromobenzoate to salicylate can be performed in the presence of catalytic amounts of $Cu(MeCN)_n^+$ complex obtained by conproportionation of Cu(II) and Cu metal in alkaline aqueous solution at r.t., with quantitative yield being obtained in the presence of tetraamine ligand (Eq. (41)) [123]



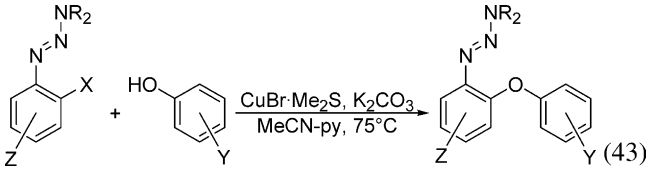
(41)

Similar results were noted in the system containing copper(I) triflate in aqueous acetone [124]. In the presence of pyridine the hydrolysis of *o*-chlorobenzoic acids can be performed in aqueous solution in the presence of Cu bronze either under ultrasonic irradiation at r.t. [125] or by conventional heating at reflux [126]. The synthesis of aryl ethers of salicylic acids can be readily performed in ultrasonically activated reaction between *o*-chlorobenzoic acid and phenols in alkaline aqueous solution in the presence of Cu/CuI at r.t. [127] or by heating in aqueous solution in the presence of pyridine [128]. Various *ortho*-coordinating substituents lend assistance in the synthesis of diaryl ethers catalyzed by soluble copper complex. Reasonable yields can be obtained even with chloro-derivatives (Eq. (42)) [129].



Hal = I, Br, Cl; Z = CONHEt, $CONEt_2$, SO_2NHEt, SO_2NEt_2 (42)

Azo-group exerts a similar directive influence [130]. A more sophisticated example of such approach is an ingenious protocol using the triazene residue to facilitate and direct the reaction at *ortho*-halogen (X = Br, I) (Eq. (43)). As triazene group is easily installed at aromatic NH_2 group, and as easily uninstalled after the reaction, the utility of this protocol is rather wide. *Para*-halogens, if present, are not substituted [131].



(43)

Though this method is not catalytic with respect to copper complex, and even uses a considerable excess of it, thus resembling the conventional Ullmann chemistry, mild

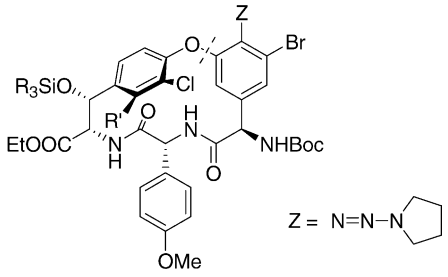
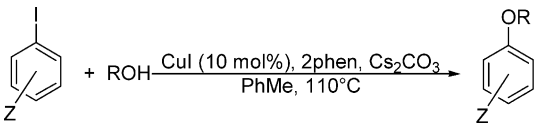


Fig. 24. Conditions: CuBr·Me_2S, K_2CO_3, py, MeCN, 80 °C.

conditions and absence of strong bases make it highly tolerant and selective, so that it has been chosen as the main macrocyclization step in the construction of complex oligopeptide based macrocyclic molecules involving ether linkages. High atropoisomeric specificity can even be achieved (Fig. 24) [131,132]. The application of this method to resin-bound triazene substrate afforded a library of variously substituted diphenyl ethers bearing *ortho*-azide group [133].

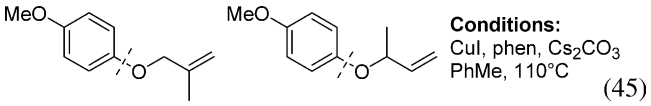
Besides phenols, aliphatic alcohols can be arylated in copper-catalyzed reactions. This reaction is likely to be less sensitive to ligand effects, as noted in a broad ligand screening study performed for the reaction of 4,6-dimethyl-2-bromoaniline with NaOMe in the system CuCl (5 mol%), L, dioxane, 100 °C; good yields (over 60%) were obtained with more than 10 different 2-, 3- or 4-substituted pyridines. The highest yields, close to quantitative, were obtained for 2-aminopyridine and its derivatives [116]. In the same system, alkoxylation with simple primary alcoholates (ethylate, butylate) is also possible, though secondary and tertiary alcoholates failed to give reasonable yields.

A much more general protocol which affords aryl ethers for a wide scope of aliphatic alcohols, normal and branched, saturated and unsaturated, employs CuI and 1,10-phenanthroline ligand (CuI, phen, Cs_2CO_3, 110 °C) in excess alcohol or in toluene for less common alcohols (Eq. (44)) [134].



(44)

The method is extremely selective. Both primary and secondary alcohols can be used, which clearly distinguishes this method from Pd-catalyzed reaction, in which secondary alcohols give side products due to ready PdH elimination. Allylic alcohols give the ethers without allylic rearrangement, even for alcohols with a terminal double bond, which are extremely liable to rearrangements, as e.g. in (Eq. (45))



(45)

Full retention of configuration is observed, as in the example in Fig. 25.

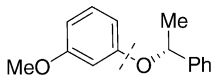
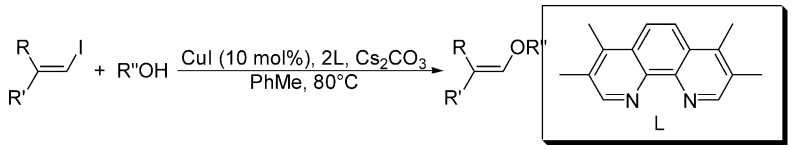


Fig. 25. Conditions: CuI, phen, Cs_2CO_3, PhMe, 110 °C.

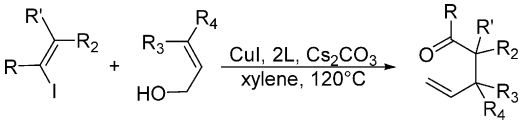
This method has been employed for the preparation of a wide range of monoethers of resorcinol with secondary aliphatic alcohols, and it has been shown to be equally suitable for the preparation of phenyl ethers, and benzyl ethers. The latter after hydrogenolysis can be converted to phenols, which is an indirect way for mild hydrolysis of iodoarenes [135].

Alkoxylation of alkenyl halides is a convenient route to vinyl ethers. In an earlier study, vinyl iodides were methoxylated by MeONe in the presence of CuBr [136]. More general protocol described by Buchwald and Nordmann [137] use CuI/phenanthroline, or better 3,4,7,8-tetramethyl-1,10-1,10-phenanthroline (Eq. (46)). Full retention of configuration is observed to show that the reaction mechanism is not the nucleophilic vinylic substitution.



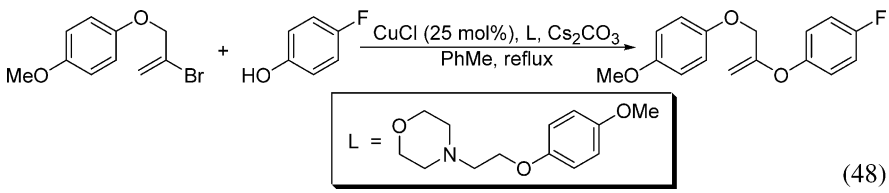
(46)

With allylic alcohols, the alkenylation can be coupled with Claisen rearrangement in a one-pot procedure leading to γ-enones (Eq. (47)) [137]



(47)

An alternative protocol uses 25 mol% CuCl in the presence of Cs_2CO_3 in refluxing toluene. The reaction can be done in the absence of ligands, but is strongly accelerated by various ligands, such as dipivaloylmethane, *N*-methylmorpholine, and *N*-(2-(4-methoxyphenoxy)ethyl)morpholine. All three ligands were declared as roughly equal in efficiency [138]. The reaction is highly selective and can be used to selectively perform the synthesis of aryloxyalkenes with multiply substituted alkenyl bromides without the loss of configuration of migration of double bond, as e.g. in (Eq. (48))



(48)

Arylations of aminoalcohols at nitrogen has been considered above. A full reversal of chemoselectivity is achieved by using Cs_2CO_3 as base in nitrile solvent (Fig. 26) [54].

5. C–S bonds

The synthesis of diaryl sulfides under the conditions of classical Ullmann reaction is well known, and as in other instances of this chemistry, suffers from harsh conditions and low functional group tolerance, though generally the methods are milder than the respective procedures for the formation of C–N and C–O bonds. Careful optimization of conditions of copper-catalyzed arylation of thiols using different solvents like DMF, DMSO, HMPA, NMP, diglym, etc. [139–144] can lead to relatively mild procedures, e.g. systems: Cu_2O, quinoline or pyridine-quinoline, 150–160 °C suitable for rather sensitive tasks such as the construction of polyarylsulfide dendrons [145], oligo(phenylene sulfides) [146]. On the other hand, microwave heating allows for faster reactions, thus bringing negative effect of harsh heating to minimum, and allowing for the extension of the scope to electron-rich aryl bromides (system CuI (10 mol%), Cs_2CO_3, NMP, microwave heating 2 h) [147].

The application of phosphazene bases was shown to enable effective formation of diaryl sulfides from thiophenols and aryl iodides at moderate temperature [148]. The reaction is highly selective allowing for the use of functionalized, electron-rich and other sorts of challenging substrates, as e.g. in Fig. 27.

However, a stoichiometric amount of copper salt and an excess of very expensive base make this approach uneconomical. If phosphazene is regarded as a special base the role of

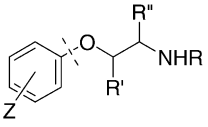


Fig. 26. Conditions: CuI (5 mol%), Cs_2CO_3, PrCN, 125 °C.

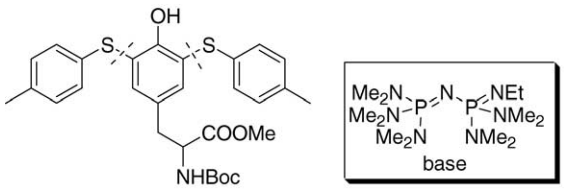


Fig. 27. Conditions: CuBr (1 eq), base (shown in the box), PhMe, reflux.

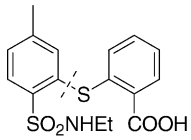


Fig. 28. Conditions: $Cu(MeCN)_4PF_6$ (5 mol%), Cs_2CO_3, PhMe, reflux.

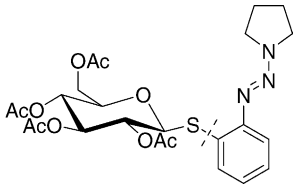


Fig. 29. Conditions: $CuBr{\cdot}Me_2S$, K_2CO_3, py, MeCN, 80 °C.

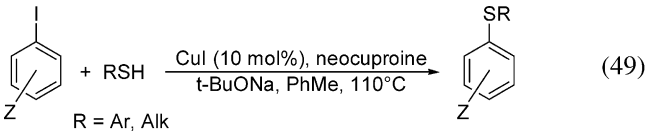
which is to form the reactive "naked" nucleophile anion, this method belongs to the domain of classical Ullmann reaction. However, phosphazene can apparently serve as a chelating ligand for copper that is more likely to account for the effect of this base.

One of the earlier efforts to develop an effective catalytic copper-catalyzed procedure utilized a soluble copper complex $Cu(MeCN)_4PF_6$ in the presence of Cs_2CO_3 as an obligatory base in toluene, in order to effect cross-coupling between thiophenols and iodoarenes bearing *ortho*-substituents capable of coordination to metal, as e.g. in Fig. 28 [129].

It could be tentatively speculated that *ortho*-functional groups facilitate the reaction by serving as ligands for copper. Unfortunately, no control experiments, showing whether such functionality is indeed required in order to perform the arylation, have been made.

The application of auxiliary triazene residue to direct the copper-catalyzed arylation of phenols has been described above. The same idea works also for the formation of C–S bonds [131]. This method has been used for the preparation of a wide range of arylthioglycosides from 1-thiosugars and iodoarenes bearing such auxiliary (Fig. 29) [149].

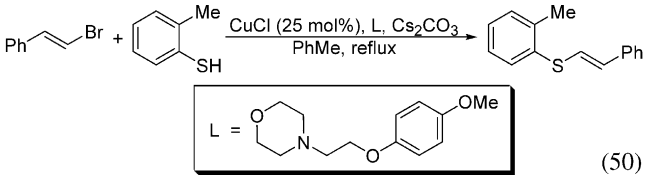
Arylation of aryl or alkyl thiols by aryl iodides can be done using CuI (10%) in the presence of neocuproine. Pre-formed catalyst is as effective, while no reaction can be observed without ligand. NaOtBu or K_3PO_4 effectively serve as bases, whereas Cs_2CO_3 is inferior (Eq. (49)). Aryl bromides are not reactive [150].



(49)

A base-free procedure can be achieved if disulfides are used as a source of ArS group in the presence of magnesium metal, similar to the procedure developed for the synthesis of diarylselenides (system CuI (10 mol%), bipyridine, DMF, 110 °C) [151].

Moderate yield of alkenylsulfide has been obtained in the reaction of β-bromostyrene with *o*-methylthiophenol in the presence of morpholine derivative as ligand (Eq. (50)). No attempts to optimize the conditions, widen the scope, or search for more common ligands have been made [138].



(50)

Besides sulfides, the copper-catalyzed arylation can be applied to the synthesis of sulfones. Catalytic protocol requires (CuOTf)·2PhH in DMSO in the presence of CyDA or DMEDA ligands (Eq. (51)) [152].

$$\mathrm{ArI} + \mathrm{MeSO_2Na} \xrightarrow[\text{DMSO, 11 °C}]{\text{(CuOTf)}_2\cdot\text{PhH (5 mol\%), 2DMEDA}} \mathrm{MeSO_2Ar} \quad (51)$$

The conventional Ullmann type procedure can be run under comparable conditions, but with cheaper copper salt (CuI, DMF, 110 °C), though used in stoichiometric amount. With haloacetylenes the sulfination can be run even at r.t. under sonication [153,154].

6. C–Se bonds

Several useful protocols have been recently developed for the cross-coupling of aryl halides and aryl selenides. The reaction of PhSH with aryl iodides can be performed in the system CuI (10 mol%), neocuproine (or preformed complex Cu(neocuproine)(PPh_3)Br), *t*-BuONa, PhMe, reflux. It is of interest that *t*-BuOK is ineffective for this reaction, while K_3PO_4 can be used though is inferior to *t*-BuONa [155]. The use of other precursors of PhSe group enables us to achieve base free procedures. Diphenyldiselenide PhSeSePh can be used in the reaction with aryl iodides, catalyzed by copper iodide or oxide (other Cu salts including CuOTf, CuCl, CuBr, $Cu(OAc)_2$, etc.) in the presence of 2,2′-bipyridine ligand and reactive metals (Mg, Zn, Al, Sm), of which Mg gave superior results (Eq. (52)) [151,156].

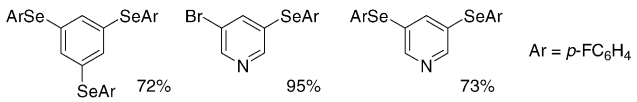
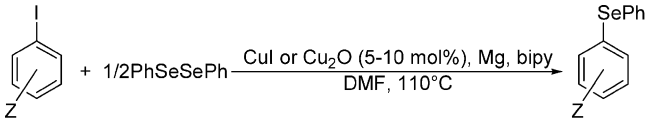


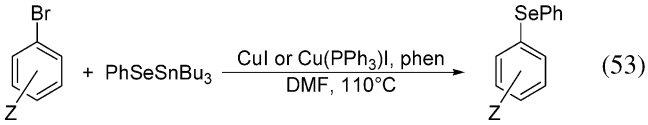
Fig. 30. Arylselenides obtained by cross-coupling protocol shown in Eq. (53).



(52)

The intermediacy of PhSeCu complex, which readily reacts with aryl iodides to form diarylselenides, has been demonstrated.

The use of tin selenides $ArSeSnBu_3$ allows for the use of less reactive aryl bromides into the arylselenation reaction. The reaction is catalyzed by either CuI or Cu(PPh_3)I complex in the presence of phenanthroline (10 mol% each) in DMF at 110 °C to give unsymmetrical selenides in high yields for both electron rich and electron poor aryl and heteroaryl bromides (Eq. (53)) [157].



(53)

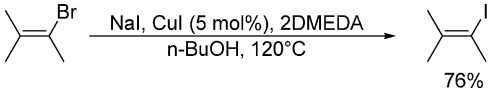
For polybromoarenes stepwise substitution of bromine is possible to yield either mono- or polyselenides, e.g. those shown in Fig. 30.

7. C–halogen bonds (halide exchange)

The exchange of bromine by iodine at an sp^2-carbon (formally it can be treated as the arylation of iodide by aryl bromides, and thus belongs to the scope of this review) is a useful method, allowing for more reactive iodides to be obtained from the more readily available bromides. Commonly, it can be done by the reaction with stoichiometric amount or excess of CuI in DMF or other polar solvents at high temperatures, though in some cases, e.g. in bromine–iodine exchange in haloacetylenes, the reaction can be performed under mild conditions [153]. Bromine to chlorine exchange in alkenyl bromides is effected in solventless reaction with stoichiometric CuCl·PPh_3 complex at high temperature [95,158]. Ligand-assisted reaction allows for this process to be performed under milder conditions, with catalytic amount of copper salt and NaI as stoichiometric source of iodine (Eq. (54)) [159].

$$\mathrm{ArBr} \xrightarrow[\text{dioxane, 110 °C}]{\text{NaI, CuI (5 mol\%), 2DMCyDA}} \mathrm{ArI} \quad (54)$$

Halide exchange can be performed also with alkenyl bomides, as e.g. in (Eq. (55))

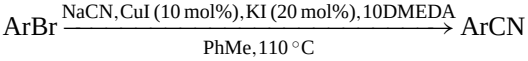


(55)

8. C–C bonds

8.1. Cyanation

The exchange of halogen for cyano group by copper(I) cyanide, the Rosenmund–von Braun reaction, is a classical method of organic synthesis. The reaction is performed by prolonged heating with a stoichiometric amount or excess of CuCN in polar solvents at high temperatures. Though this is a reliable method with a long and impressive history of successful application in organic synthesis, similarly to other Ullmann type processes, a milder protocol is desirable. The first such method has recently appeared for cyanation of aryl and heteroaryl bromides. The reaction involves exchange of bromine by iodine. As other ligand assisted methods, this reaction shows a high degree of tolerance to functional groups. However, the reaction is air and moisture sensitive, and requires a huge amount of rather expensive ligand (Eq. (56)) [160].



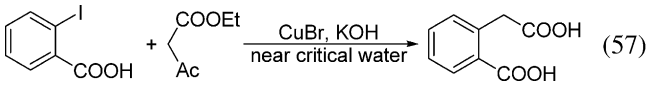
(56)

8.2. The arylation of CH-acids

The Hurtley reaction [161] is a well established method for the arylation of CH-acids in the presence of copper or copper salts (the canonical procedure is published in Organic Syntheses [162]). The scope of reaction is very narrow, as only *o*-bromobenzoic acid and its close relatives, aromatic acids with proximal bromine atom, are reactive [163–168]. The reaction takes place under mild conditions (originally, sodium enolate of acetylacetone, catalytic Cu bronze, reflux in EtOH; in later works variations of original procedure used other systems as e.g.: free acetylacetone, Cu bronze, *t*-BuOK, *t*-BuOH, reflux [169], or CuBr (<10 mol%), PhMe, reflux [170]), so uncommon for other Ullmann type chemistry. Apparently, the ease of Hurtley reaction is associated with a special type of substrate, which can serve as chelating ligand for copper. As early as 1929, this reaction revealed that copper(I) catalyst can possess a remarkable efficiency under rather mild conditions, that this chemistry is not forever condemned to overheating and other notorious symptoms of conventional Ullmann chemistry. Thus, the Hurtley reaction should be regarded as an early prototype for mild and efficient copper-assisted chemistry that has developed in the last decade.

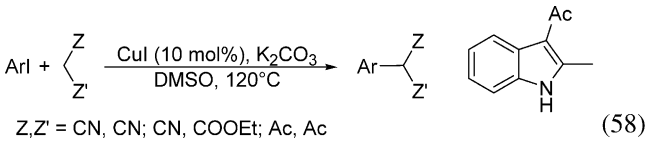
The Hurtley reaction is applicable not only to *o*-halobenzoic acids, but similar derivatives of heterocycles, such as pyridine, thiophen [169,170], benzofuran [171], etc.

A green version of the Hurtley reaction has been achieved in subcritical water in pressurized reactor under microwave heating. Deacylation and saponification of the arylation product occurred (Eq. (57)) [172]



(57)

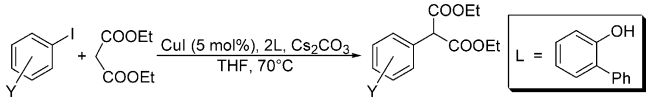
Earlier examples of Cu-mediated arylation of CH-acids by non-chelating aryl halides are well known to share common deficiencies of Ullmann chemistry (stoichiometric Cu, high temperatures in polar solvents, poor reproducibility, good yields are usually obtained only for aryl halides bearing electron-withdrawing substituents) (e.g. [173–176]). A milder protocol was developed in 1993 to employ CuI (10 mol%), K_2CO_3, in DMSO at 120 °C to perform the arylation of such CH-acids as ethyl cyanoacetate, malonodinitrile, acetylacetone [177]. Other Cu sources as CuBr, CuCl, Cu_2O, $Cu(OAc)_2$ are almost equally effective. The reaction of acetylacetone with *o*-iodoaniline is accompanied by cyclization to give indole derivative shown in Eq. (58).



(58)

Though this method avoids explicit use of ligands, it might be argued that any of CH-acids used under basic conditions might themselves furnish ligand assistance to form copper chelates. The addition of other ligands, e.g. Ph_3P or amines inhibit the process, certainly because excessive strong ligands overload the coordination sphere of copper.

Further development of this method has led to a still milder protocol employing phenols as supporting ligands, the best of which was *o*-phenylphenol. Cs_2CO_3 can be replaced by K_3PO_4, though the latter is less efficient (Eq. (59)) [178]. In spite of explicit use of ligands, copper enolates are likely to play an important role in this reaction, as Meldrum acid, the cyclic malonate ester which is not capable of forming six-membered metal chelates, is inert under the described conditions.

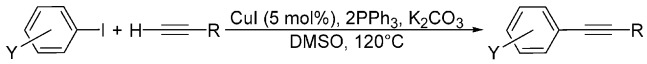


(59)

8.3. The cross-coupling with terminal acetylenes

Cross-coupling of aryl or alkenyl halides or triflates with terminal acetylenes (the Sonogashira–Hagihara reaction) is among the fundamental methods of Pd-catalyzed C–C bond

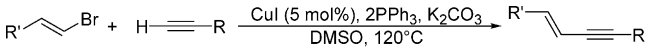
forming reactions. The addition of Cu(I) salts is usually required in this reaction, so that Cu–Pd co-catalysis is considered a standard requirement for this method, and copper-free protocols are quite rare. The role of copper is believed to be involved in the formation of copper acetylides, which in their turn react with electrophilic coupling partner through a palladium-catalyzed process. As copper acetylides are themselves able to react with organic halides (the Castro–Stephens reaction [179,180]), a palladium-free copper-catalyzed version of this reaction also exists. Alkenyl bromides and iodides were found, in 1989, to react with terminal acetylenes in the presence of stoichiometric amounts of CuI [181]. A truly catalytic version followed soon. Cu-catalyzed Sonogashira reaction of terminal acetylenes with aryl iodides (bromides are generally unreactive) runs smoothly in the system CuI (5 mol%, CuCl, CuBr and $Cu(OAc)_2$ are similarly effective), K_2CO_3, PPh_3 in DMSO or DMF at 120 °C under N_2 (Eq. (60)) [182,183].



(60)

It is interesting to note that while in the standard Pd/Cu-catalyzed Sonogashira reaction tertiary amines are the most commonly used bases [184], in Cu-catalyzed version amines usually inhibit the reaction.

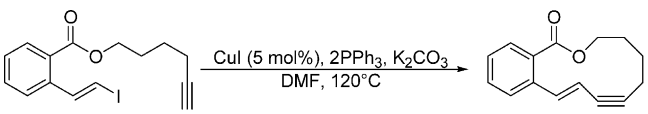
Alkenyl bromides or iodides under such conditions give enzymes with full retention of stereochemistry (Eq. (61))



(61)

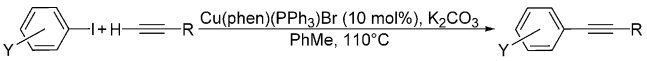
In the presence of CO, the insertion leading to arylacetylenyl- or alkenylacetylenylketones takes place, though the competition between simple and carbonylative cross-coupling cannot be fully resolved in favor of carbonylation.

The method has found application in synthesis, as e.g. for cross-coupling of 2-iodoindole with propiolic ester [185], and macrocyclization (Eq. (62)) [186]



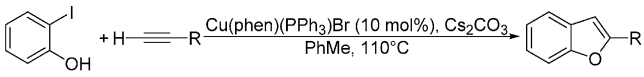
(62)

An alternative protocol uses preformed Cu(I) complexes, which allows for the use of a more convenient solvent toluene in place of DMSO or DMF [30]. The use of preformed complex is essential as the mixture of CuBr and 1,10-phenanthroline gave no reaction (Eq. (63)).



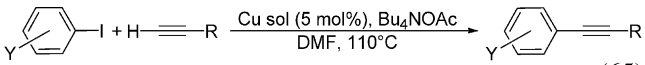
(63)

Neocuproine and bipy complexes are much less effective. Later the method was further optimized and the best catalyst fount to be the cationic copper complex $[Cu(phen)(PPh_3)_2](NO_3)$ [187]. With *o*-iodophenols this protocol can lead to benzofurans in high yields (Eq. (64))



(64)

Copper nanoparticles protected by tetraoctylammonium cations have been recently found to catalyze Sonogashira-type cross-coupling of iodoarenes and activated bromoarenes with terminal acetylenes. The reaction is accomplished in the absence of ligands. Nanoparticles under the reaction conditions described were stable enough to survive three times of successive re-charging of new reactants, thus giving an overall TON value of 73, a rather high number for copper catalysis (Eq. (65)) [188]. This reaction establishes an interesting precedent of Sonogashira-type cross-coupling catalyzed by zero-valent Cu, which would be an exact analogy with standard Pd-catalyzed reaction.

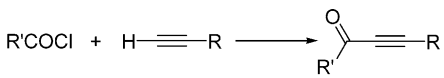


(65)

The use of copper catalyst affords e.g. vinylsubstituted compounds from *p*-vinylphenylacetylene without a risk to invoke the Heck reaction [187]. Under the same conditions *o*-iodoanilides afford indoles [189].

The use of diaryl or alkenylphenyliodonium salts allows for the arylation of terminal acetylenes to be performed under very mild conditions in the absence of ligands (CuI (10 mol%), $NaHCO_3$, DME–H_2O, r.t.) [190].

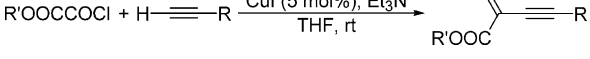
Cross-coupling of terminal acetylenes with acid chlorides is a convenient direct route to acetylenic ketones. CuCl or CuI (10 mol%) catalyzes the reaction of acid chlorides with terminal acetylenes in the presence of Et_3N in toluene at 80 °C or reflux [191,192]. The use of Et_3N as solvent allowed this reaction to be performed at r.t. [193], or, if a fast result is desired, under microwave heating (Eq. (66)) [194]:



(66)

Method A: CuI or CuCl (10 mol%), Et_3N, PhMe, 80°C
Method B: CuI (5 mol%), Et_3N - solvent, r.t. or μW oven

Cross-coupling of terminal acetylenes with monooxalyl chlorides giving acetylenic ketoesters is best performed in THF (Eq. (67)) [195]



(67)

An alternative route to arylalkynylketones is the carbonylative cross-coupling of terminal acetylenes with diphenyliodonium salts in the atmosphere of CO, which can readily be carried out in the presence of 10 mol% CuI and $NaHCO_3$ at 30 °C [196].

8.4. The cross-coupling with organometallic compounds

Today, cross-coupling is universally acknowledged as a realm of palladium catalyzed reactions. However, the organocuprates were the first to establish the cross-coupling as a vital method in organic synthesis [3–6]. Since then, the organocuprates have lost the lion's share of this field to palladium-catalyzed cross-coupling, because the organocuprate chemistry is largely non-catalytic, requires special conditions, and is much less tolerant to conditions, functionality, experimental skills, etc. Still, as in other cross-coupling areas, there is an ample evidence that copper is able to perform well in catalytic cross-coupling C–C bond forming reactions, and some Cu catalyzed protocols have already been developed.

8.4.1. Cross-coupling of Grignard reagents and organozincs

In the pre-history of transition metal catalyzed cross-coupling, the effect of copper salts on the reactions between Grignard reagents and organic halides has been disclosed in the seminal works first by Kharash, and then by Tamura and Kochi [197]. Copper-catalyzed cross-coupling with sulfonate esters was also reported quite early on [198]. These methods commonly employ CuI in substoichiometric amounts, or, better Li_2CuCl_4 in catalytic amounts (3–5 mol%) in THF at r.t. or below. Under the conditions of reaction Cu(II) in this precursor is apparently reduced to Cu(I) state, so the respective salt CuCl·2LiCl can also be used, in some cases even with better results [199]. Several reports describe the use of CuBr, e.g. for cross-coupling with ω-bromoalkylnitriles[200], or benzyl-aryl cross-coupling [201]. The system CuBr–HMPA has been proposed for the coupling of α,ω-dibromoalkanes with aryl or vinyl Grignard reagents (particularly sterically hindered ones), with either one or two bromines being selectively replaced (Fig. 31) [202,203].

A new soluble catalyst system CuBr–Me_2S–LiBr–PhSLi has been developed and has shown remarkable performance for cross-coupling of primary alkyl tosylates or mesylates with a wide scope of Grignard reagents including aliphatic, vinylic, and aromatic ones. Reasonable yields can be obtained with secondary and tertiary substrates. The addition of HMPA allows for the application of elevated temperatures in order to force some reluctant substrates to react [204]. This method has been effectively used for the construction of cyclophane architectures (Fig. 32) [205], as well as for alkyl–alkyl coupling [206].

The most popular catalyst so far has been Li_2CuCl_4. Alkenyl and aryl groups can be transferred this way (e.g.

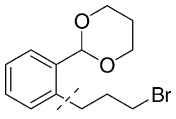


Fig. 31. Conditions: CuBr (10 mol%), THF–HMPA, reflux.

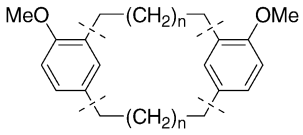


Fig. 32. Conditions: CuBr–LiBr–Me_2S–PhSLi, THF–HMPA, reflux.

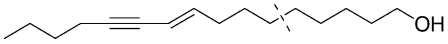
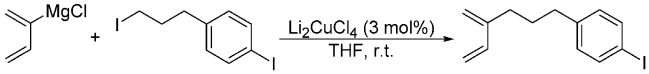


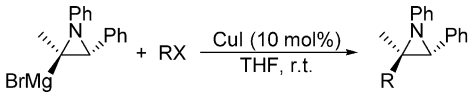
Fig. 33. Conditions: CuI (30 mol%), THF, r.t.

[207,208]). In the case of substrate with both aryl or alkyl sites, the latter are more reactive allowing for chemoselective substitution, orthogonal to what should have taken place if Pd catalyst were utilized (Eq. (68)) [209]



(68)

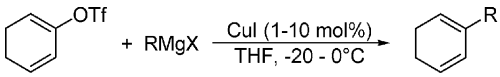
Magnesiated aziridines give cross-coupling products with full retention of configuration (Eq. (69)) [210].



(69)

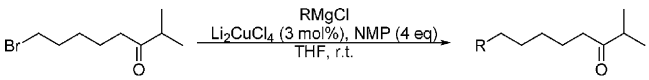
Copper-catalyzed cross-coupling or Grignard reagents are particularly suitable for the alkyl–alkyl or allyl–alkyl coupling, the reactions in which Pd catalyzed cross-coupling methods have been so far notoriously ineffective. Examples in syntheses are numerous, a recent one being exemplified in Fig. 33 [211–215].

Dienyl triflates effectively couple with Grignard reagents (primary and secondary alkyl, allyl, phenyl) in the presence of catalytic amounts of CuI or ate complex CuCl·2LiCl under very mild conditions. The reaction shows a high catalytic efficiency, almost unprecedented in copper catalysis, since as low as 1 mol% of copper salt is enough (Eq. (70)) [216–229].



(70)

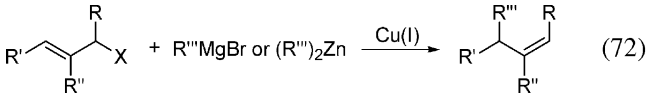
One serious disadvantage of cross-coupling reactions using reactive organometallics, such as Grignard reagents, is the restriction on functionality in the second coupling partner. The addition of NMP turned out to relieve this restriction, and allowed for the use of halides and tosylates with carbonyl, alkoxycarbonyl and similar groups (Eq. (71)) [230]



(71)

The other advantage of using NMP as an additive is the possibility of performing high-yield cross-coupling with *tert*-alkyl Grignard reagents, which ordinarily either do not react at all or produce miserable yields [230].

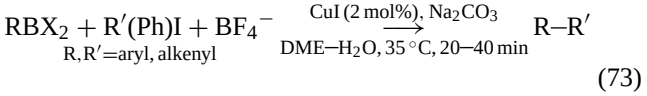
Allylic substrates (halides or esters including acetates, perfluorobenzoates, sulfonates, phosphates, etc.) readily participate in a number cross-coupling reactions Grignard or organozinc reagents in the presence of copper(I) derivatives, usually in catalytic quantities (Eq. (72)) [219,229]. These reactions usually involve the allylic rearrangements (S_N2' substitution) and are highly stereoselective. By an analogy with palladium catalyzed allylic substitution reactions (the Tsuji-Trost reaction and related methods), π-allylic complexes of copper are likely to be involved. Such reactions are not classified as cross-coupling, and thus will not be discussed here.



(72)

8.4.2. Cross-coupling of organoboron compounds

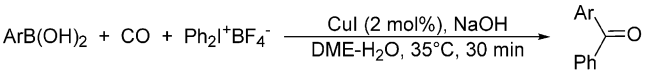
So far, the application of copper-based catalysts for cross-coupling reaction of organoboron compounds remains practically unexplored. However, there are indications that this might be possible. Copper metal nanoparticles were found to catalyze the reaction between $PhB(OH)_2$ and PhI in the presence of K_2CO_3 in DMF at 110 °C, though mixed Pd–Cu nanoparticles performed much better [231,232]. With diaryliodonium salts as electrophilic coupling partners CuI showed good catalytic activity under very mild conditions in the reaction with boronic acids, boronates or boranes (9-alkyl-9-borabicyclononanes (9-BBN)) (Eq. (73)) [233].



(73)

Both these observations show that Cu is capable of both oxidative insertion at least to C–I bonds, and further transmetallation of organocopper intermediate with boronates or boranes. The ease of reaction with diaryliodonium salts, which are highly reactive in the oxidative addition, shows that the transmetallation step can indeed be very effective. Thus, it might be concluded that an efficient protocol for copper-catalyzed version of the Suzuki reaction could indeed be developed in the near future.

In the presence of CO, the reaction of diphenyliodonium salt with arylboronic acids leads to benzophenones, the products of CO insertion (Eq. (74)) [233].



(74)

This reaction highlights the fundamental similarity of copper-catalyzed cross-coupling chemistry to palladium-catalyzed chemistry, and further corroborates the hypothesis that these two chemistries share the same type of catalytic cycle.

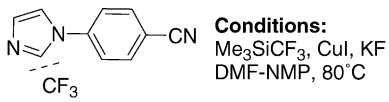


Fig. 34. Conditions: Me_3SiCF_3, CuI, KF, DMF–NMP, 80 °C.

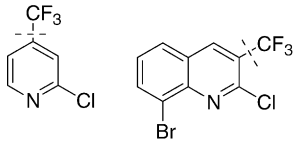
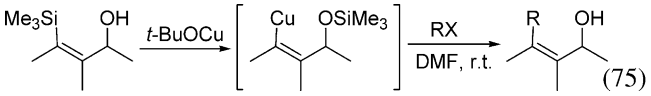


Fig. 35. Conditions: Me_3SiCF_3, CuI, KF, NMP, r.t.

8.4.3. Cross-coupling of organosilicon compounds

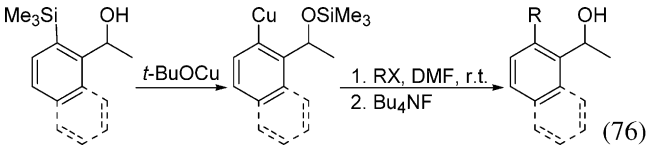
There are a few specific protocols of cross-coupling reactions of organosilicon compounds with organic halides, assisted by Cu(I). Though the role of Cu(I) in these reactions is evidently catalytic, current protocols require stoichiometric amounts of Cu(I), likely because the regenerated form of Cu(I) is not reactive enough to effect the next cycle.

A neighboring oxygen atom may facilitate transmetalation: γ-trimethylsilylallylic alcohols undergo transmetallation with *t*-BuOCu giving rise to the respective alkenylcoppers, which directly react with allyl, benzyl, and primary alkyl halides in a stereospecific fashion with full retention of configuration (Eq. (75)). Reactions with aryl or alkenyl halides require Pd(0) catalysis [234,235].



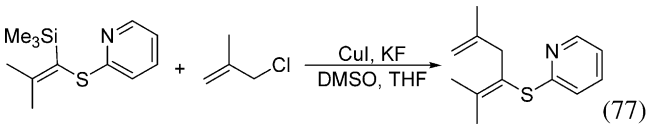
(75)

The method has been recently extended to aromatic series (Eq. (76)) [236]



(76)

A similar approach using directing pyridyl residue has been proposed (Eq. (77)) [237]



(77)

Trifluoromethylation by Me_3SiCF_3, induced by CuI in the presence of KF, is a useful protocol proven in a number of applications [238], e.g. for introduction of CF_3 group to imidazoles (Fig. 34) [239].

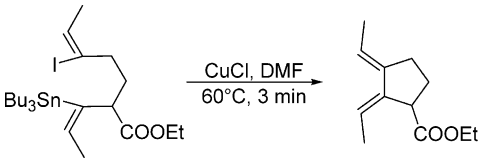
In these reactions only iodine is reactive, while Cl or Br atoms, even at more reactive positions, are retained (Fig. 35) [240].

Cross-coupling of terminal acetylenes or their silylated derivatives with Ph_3BiF_2 reagent is catalyzed by CuCl. Organobismuth(V) compound in this reaction is an electrophilic coupling partner [241].

8.4.4. Cross-coupling of organotin compounds

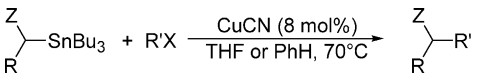
In the palladium-catalyzed cross-coupling of organotin compounds (the Stille reaction) the positive influence of copper(I) is well known [242], which allows us to accelerate sluggish reactions, particularly important for reactions with geminally substituted alkenyltin compounds. There are arguments in favor of the hypothesis that copper salts perform the role of ligand scavengers, thus facilitating the operation of palladium complexes by freeing the coordination sites necessary for the complexation of reactants [243]. However, as in the case of cross-coupling with terminal acetylenes, the transmetallation leading to intermediate organocopper species, which take part in the palladium driven catalytic cycle, is a highly probable general mechanism. Anyway, organocopper compounds could not be formed by transmetallation, copper driven palladium free catalysis would not be possible. Transmetallation of tin to copper has been reported to take place only in highly polar solvents like NMP [244].

The palladium free copper-catalyzed version of Stille reaction turned out to be a very convenient procedure. Intramolecular version can be achieved by CuCl in DMF solution on gentle heating, and is extremely fast and selective (Eq. (78)) [245].



(78)

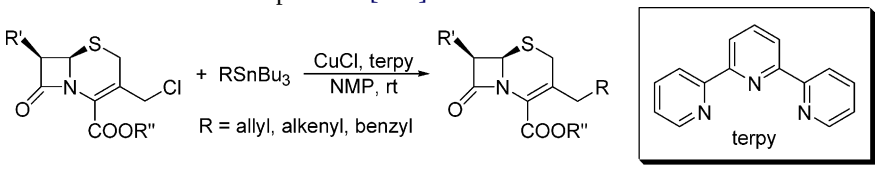
Intermolecular versions are also well known. Alkenyltins can be reacted with allylic halides in the presence of CuI at r.t. in DMSO–THF [246]. Similar reactions were shown to take place with thienyl or furyltins [247]. Enol triflates were identified as possible coupling partners [248], though this reaction is limited to specific cases [249]. Transmetallation can be facilitated even in the absence of polar solvent by proximal coordinating groups (Eq. (79)) [250,251].



(79)

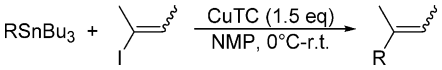
Z = OAc, OCH_2OMe, PhOC(S), MeC(S), etc.
R' = allyl, propargyl, Ph, acyl, etc.

In most reported cases of C–C cross-coupling no ancillary ligands are used, and copper(I) is introduced as simple salts (CuCl, CuI, CuCN, etc.). Positive influence of bidentate and particularly tridentate ligands (bipyridine and terpyridine) on Cu(I) catalyzed cross-coupling has been noted (Eq. (80)). Interestingly, this reaction can as well be promoted by Cu powder in the presence of the same ligands, though at elevated temperature [252].



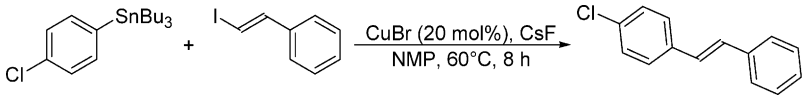
(80)

So far, the most useful protocol has been described by Allred and Liebeskind [253]. Copper(I) thiophene-2-carboxylate (CuTC) promotes very fast cross-coupling of aryl or alkenyltin compounds with alkenyl iodides at r.t. or even below (Eq. (81)) [253].



(81)

The need for high loadings of copper salt is accounted for by reversibility of transmetallation step, which leads to inhibition of cross-coupling reaction. In the presence of tin scavengers, such as alkali metal chlorides or fluorides, a catalytic version can be achieved in some cases, at the expense of reaction rate. In catalytic version CuBr or CuI can be used in place of CuTC, in DMF or NMP at 60–90 °C (Eq. (82)) [253,254]. Catalytic version is applicable to the coupling of aryl, alkenyl, or heteroaryltin compounds with alkenyl or aryl iodides, e.g.



(82)

The protocol is applicable to polymer bound aryl iodides [255]. Iodoalkynes can however be cross-coupled with organotin compounds under milder conditions, at r.t. in the presence of 10 mol% CuI [256]. Besides iodides, tellurium(V) derivatives can be used in copper catalyzed cross-coupling with organotin compounds [257].

Still, the protocol of using a stoichiometric or overstoichiometric amount of CuTC enjoys a good level of popularity in complex organic synthesis, obviously because of remarkable mildness, unsurpassed rate and high tolerance to functionality, geminal substituents, and double bonds liable to migration (Fig. 36) [258,259], see also [260].

Copper-catalyzed cross-coupling works much faster and under milder conditions, as e.g. in the following example in which the use of copper catalyst in place of palladium catalyst allowed one to shorten the reaction time from 18 h to less than an hour (Fig. 37) [261].

The reaction can be run under very mild conditions, at temperatures below zero, to afford cross-coupling products of

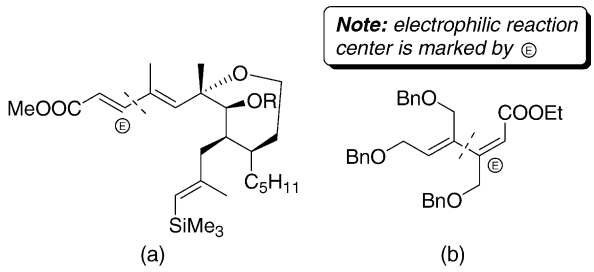


Fig. 36. Conditions: (a) CuTC, $Ph_2P(O)OBu_4N$, NMP and (b) CuTC, NMP.

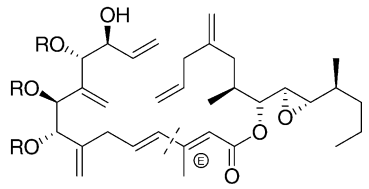


Fig. 37. Conditions: CuTC, NMP, 0 °C, 45 min.

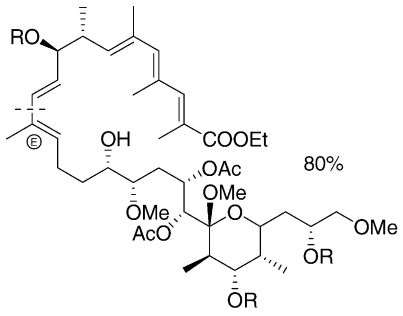


Fig. 38. Conditions: CuTC, NMP, −10 °C, 1 h.

high complexity, in the cases where Pd-catalyzed procedures fail (Fig. 38) [262].

Unique syntheses, as e.g. simultaneous formation of two bonds leading to a macrocyclic compound in high yield can be achieved using this method (Fig. 39) [263].

Synthesis of heterocyclic compounds, particularly sulfur-containing can be achieved (Fig. 40) [264,265].

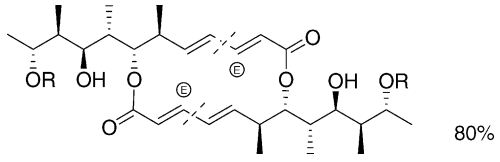


Fig. 39. Conditions: CuTC, NMP, r.t., 15 min.

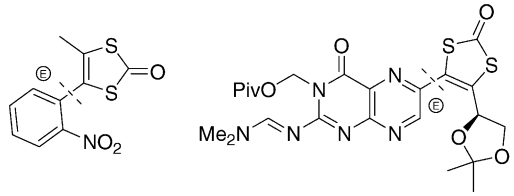
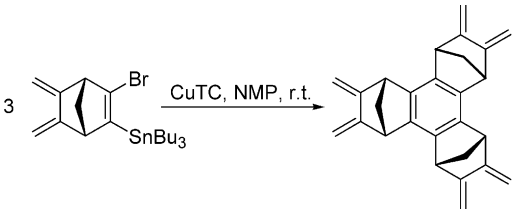


Fig. 40. Conditions: CuTC, NMP, r.t., 40 min–2 h.

Cyclotrimerization of stannylated bromoalkenes leading to a benzene ring can be effected either by $Cu(NO_3)_2{\cdot}3H_2O$ [266–271], or even better by Liebeskind's catalyst CuTC (Eq. (83)) [272–274] giving high yields of new compounds with intriguing molecular architectures. Highly reactive diene units are left intact, a result hardly expected if this cross-coupling be attempted using the regular palladium based Stille systems.



(83)

The trimer is obtained as a mixture of syn and anti isomers. An alternative technique leading to preferential formation of more valuable *syn*-trimers using the system CuI, $LiNO_3$, DMF–DME, r.t. [275].

Copper catalyzed Stille reactions have always required the iodo-derivative as an electrophile. There are indications that bromides can also react, though currently giving unacceptable yields [253,276]. Hopefully this can be optimized in further studies.

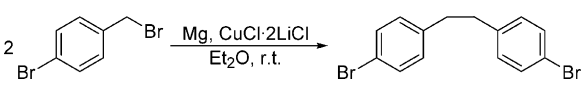
8.5. Heck reaction

Though the Heck reaction does not belong to cross-coupling chemistry, since it involves a different type of catalytic trasformation (the addition–elimination mechanism), the formal similarity to the Sonogashira reaction has often placed it in the cross-coupling domain. Copper catalysts were found to be able to catalyze the Heck reaction, though only a few reports have yet been published, using copper(II) salts supported on solid sorbents, such as modified silicas, allowing for multiple recycling of the active catalyst [277,278].

8.6. Homocoupling

Homocoupling is necessarily a redox process, and thus should not be discussed here, as it cannot be effected by Cu(I) alone in the absence of oxidizing or reducing agents. Still, a few examples of homo-coupling reactions deserve mention in the context of this review, due to their relevance to the processes. discussed.

In the presence of CuCl·2LiCl a homocoupling of alkyl or aryl halides can be performed through in situ formation of Grignard reagent (Eq. (84)). Thus, this reaction is actually a cross-coupling [199].



(84)

However, Cu(I) salts alone are known to effect homocoupling or iodo derivatives. In fact, due to accessibility of four

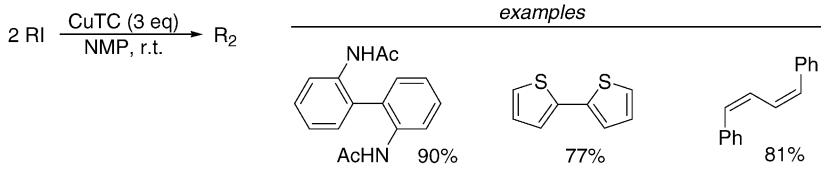
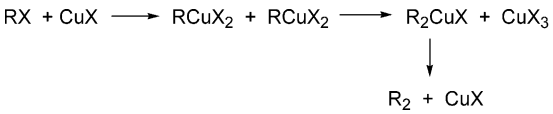


Fig. 41. The homocoupling of organic iodides in the presence of CuTC.

oxidation states from 0 to 3+ for copper, this metal can perform several roles in a homocoupling process, and no external reducing or oxidizing agent is needed. Tentatively, the scheme can be drawn like that common for the cross-coupling, but involving ligand exchange as an additional step between oxidative addition/reductive elimination (Eq. (85)).



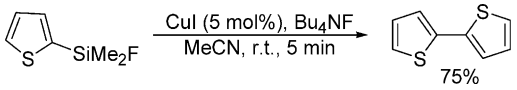
(85)

In this case, the formation of Cu(III) as one of the final products is inevitable. In order for this to become possible, a good electron-rich and preferably chelating ligand should be present.

Copper(I) triflate induces homocoupling of *o*-bromonitrobenzene or diethyl iodofumarate at r.t. in acetone in the presence of ammonia [124]. Copper thiophenecarboxylate (CuTC) can be used to perform a high-yield homo-coupling of aryl, heteroaryl or alkenyl iodides under mild conditions, given that 2.5–3 equivalents of Cu(I) are used. Aryl iodides should bear a coordinating *ortho*-substituent to take part in the reaction (Fig. 41) [279].

The actual stoichiometry of this reaction is obscure. In the absence of other counterions two copper atoms should bind iodine to form 2CuI, then the third should be released in Cu(III) form. Can it be so, and what stabilizes this oxidation state? As far as we know there is no answer so far.

Cu(I) induced homocoupling has been used to prepare thiafulvalene oligomers [280]. While the homocoupling of iodo-derivatives is a reductive process, the homocoupling of organometallic compounds requires oxidant. Again, Cu(I) alone has been discovered to be able to perform this trick as well. Thus, CuI catalyzes homocoupling of organosilicon compounds with a wide range of residues including aryl, heteroaryl (thienyl), alkenyl or alkynyl in the presence of Bu_4NF. The reaction is extremely fast at r.t. (Eq. (86)) [281]



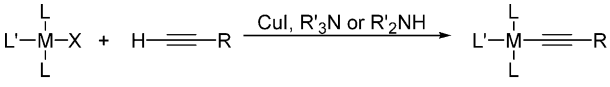
(86)

The mechanism of this reaction is obscure, as no mention of any oxidant is given and copper is used in catalytic amounts. However, in a parallel work the homo-coupling of organosilicon compounds has been shown to take place under similar conditions, but in the absence of fluoride-ion [282–284]. This reaction has been established to require air atmosphere to take place, thus being an obvious example of oxidative homo-coupling involving Cu(II) species or radicals, similar to well known Glaser–Hay homo-coupling of terminal acetylenes catalyzed by CuCl in the presence of TMEDA and oxygen as stoichiometric oxidant [285]. A similar homo-coupling of arylboronic acid in the presence of catalytic amount of Cu(I) or Cu(II) salt under oxygen atmosphere has also recently been described [286].

9. Miscellaneous

Several other reactions comply with formal definition of copper assisted cross-coupling. Hydrogenolysis of C–halogen or C–sulfonate bonds by hydrides in the presence of Cu(I) or Cu(II) can be regarded as C–H cross-coupling [287–289].

There are methods which can be used to form carbon-metal bonds. For example B to Sn transmetallation 1-trimethylsilyl-1-alkenylboranes is catalyzed by CuI, thus being an instance of C–Sn cross-coupling [290]. Transition metal–carbon cross-coupling is a well-known procedure used to prepare alkynyl complexes of Pt, Ni and some other metals (Eq. (87)) [291]:



(87)

This method is a valuable means for the construction of rod-like organometallic polymers, useful as advanced materials. The involvement of such transformations is a very likely explanation for the effect of copper co-catalysts in palladium catalyzed cross-coupling reactions, particularly the Sonogashira–Hagihara reaction ([292] and references therein).

10. Concluding remarks

Thus, it can be concluded that copper salts and complexes are indeed versatile reagents for cross-coupling reagents, with breadth of scope similar to that of palladium—from C–C, C–heteroatom (N, P, O, S, Se) to C–H and C–metal. The acceleration of the studies of copper assisted cross-coupling in the last few years is amazing. Is it then already a competitor for palladium?

Copper indeed seems to have a number of advantages over palladium. Besides the cost of metal (ca. by 10^5 cheaper [8]), copper catalysts usually employ much cheaper ligands

– while palladium prefers expensive phosphines, copper satisfy itself with more trivial N or O ligands, many of which are common analytical or general purpose reagents. Even more appealing is the fact that copper assisted methods do not exactly follow their palladium counterparts – copper apparently has its own applications, where it is superior to palladium, e.g. in better tolerance to functional groups and double bonds, and more flexible chemoselectivity (cf. C–N, C–O cross-coupling, etc.). Copper-assisted methods allow to successfully extend cross-coupling methods to some classes of processes, which are still unfavorable targets for palladium catalysts, e.g. secondary alcohols in C–O coupling, sp^3–sp^2 and sp^3–sp^3 C–C coupling.

Anyway, the list of achievements is today much shorter than a to-do list. The most essential drawback of copper assisted cross-coupling chemistry as a whole is a complete lack of understanding of the effect of ligands. The catalytic systems are usually being developed by random trials. New combinatorial approaches to the development of new catalytic systems have greatly facilitated the search; therefore it is not surprising that new methods are appearing in the last few years at a steadily increasing rate. This approach can find good systems for particular cases, but it cannot help to understand what makes such systems work, and so it can hardly help us to understand what is required for building new applications and refining the already developed ones.

We even do not know what makes the "new copper chemistry" so efficient. What is the essence of the difference between conventional Ullmann and post-Ullmann methods – the ligands, the solubility, the media, possibly even the mechanism, or something else?

Many studies in the new wave of copper-assisted chemistry concentrated on a notion of "well-defined catalysts", implying that a certain complex with well-defined coordination shell and notable ligands is put into the reaction mixture. This approach apparently tries to build a counterpart for palladium-catalyzed chemistry, where similar complexes play major roles. However, it is well known that in Pd-catalyzed chemistry the initial form of complex loaded is never the actual catalyst, which is generated in situ by a preactivation procedure and whose structure is usually unknown because of the high liability of the palladium coordination shell. The same should be true for copper chemistry. We should admit that currently nothing is known on what happens to coordination shell during the reaction. As cross-coupling requires at least two sites to be free, it is apparent that the transformations in the coordination shell should be profound.

Lots of data give clear evidence that copper is sensitive to overloading of coordination sphere with strong ligands, which often leads to inhibition of reaction. Monodentate phosphines in most cases inhibit copper catalyzed reactions, chelating diphosphines are altogether not regarded as useful ligands. In many cases, the use of soluble complexes of copper gives poorer results than the heterogeneous copper salts only sparingly soluble in the reaction media. Apparently, high solubility often implies a good ligation, in which case there is little place left in the coordination sphere of metal for transformations involved in catalysis.

The higher sensitivity of copper to ligation may account for the most essential difference between Cu and Pd in catalysis. Palladium allows for precise control of coordination sphere by phosphine and similar well-behaving strongly bonded ligands, while copper does not, and instead must rely on a fortuitous combinations of more labile ligands, thus restricting intentional control of catalytic activity. If this is indeed so, copper has few chances to ever become a peer to palladium in cross-coupling chemistry, but is forever bound to a limited role of filling few gaps in the immense cross-coupling chemistry governed by the noble metal.

Current deficiencies of copper are as apparent as its successes.

The chemistry is not so far popular. Practically, all of publications on copper-assisted cross-coupling are devoted to the development of methodology, with very few actual applications in synthesis. In order to estimate the real potential of new methods, these should be thoroughly tested by synthetic in various preparative works.

Is it really cheap? Though copper may indeed be by 10^5 cheaper than palladium, few methods can boast catalytic activity (expressed by turnover number) higher than 10. Besides, most reactions are slow to require a day or so for completion, so that turnover frequencies are very low. In Pd chemistry very high TONs exceeding 10^4 and TOFs exceeding $10^3\ h^{-1}$ are now quite usual. Thus, the actual cost of catalyst may not be so favorable for copper. To this we should add a strict preference of copper for expensive organic iodides as substrates, with bromides being much less useful, and only a few systems being devoted to organic chlorides, whereas palladium has achieved considerable success in recent years reactions with unactivated substrates.

Copper assisted cross-coupling is not so far applicable to sulfonate (triflate, tosylate, etc.) leaving groups, with the sole exception of copper-catalyzed reactions of Grignard reagents. This is a serious omission, as sulfonate esters allow one to introduce the large field of phenols and carbonyl compounds into cross-coupling; palladium catalysts serve excellently in such chemistry.

The copper assisted chemistry is environmentally unaware. One of the most evident trends in organic synthesis today is environmental awareness, definitely a must for any chemistry that aims at large scale applications. In copper assisted chemistry practically no efforts to develop green methods can be found. Meanwhile in Pd-catalyzed chemistry a lot of successful ideas on clean media, recyclable systems, highly effective catalysts, etc. have already been implemented [293].

It could however be hoped that these deficiencies are temporary, easily pardonable by the youth of the field, and soon to be discarded during active future development. Then there comes the Renaissance.

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