Coupling Reactions

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Catalytic C−C, C−N, and C−O Ullmann-Type Coupling Reactions

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Copper-catalyzed Ullmann condensations are key reactions for the formation of carbon–heteroatom and carbon–carbon bonds in organic synthesis. These reactions can lead to structural moieties that are prevalent in building blocks of active molecules in the life sciences and in many material precursors. An increasing number of publications have appeared concerning Ullmann-type intermolecular reactions for the coupling of aryl and vinyl halides with N, O, and C nucleophiles, and this Minireview highlights recent and major developments in this topic since 2004.

1. Introduction

The copper-mediated arylation of amines,[1] phenols[2] (Ullmann condensations), amides, carbamates[3] (Ullmann–Goldberg condensations), and activated methylene compounds[4] (Ullmann–Hurtley condensations) are well-documented methods that were discovered several decades before the palladium- and nickel-catalyzed procedures. For more than a century they were some of the most useful and practical methods for the formation of C(aryl)−N, C(aryl)−C, and C(aryl)−O bonds.[5–10] Such copper-mediated coupling reactions have numerous industrial applications, including the synthesis of intermediates as well as synthetic targets for the life sciences and polymer industries. However, Ullmann-type coupling has not been employed to its full potential for a long time. Up until 2000, the synthetic scope of these transformations was restricted because of the often harsh reaction conditions, limited range of suitable substrates, and the moderate yields obtained. The condensations were usually conducted in high-boiling polar solvents such as *N*-methylpyrrolidone, nitrobenzene, or dimethylformamide, at temperatures as high as 210 °C, often with stoichiometric amounts of copper reagents. Aryl halides activated by electron-withdrawing groups or containing *o*-carboxylic acid groups were preferentially used.[11] However, some reported studies had revealed rate enhancements when the arylations were conducted in the presence of ligands for the copper center or of other additives.[12] These latter compounds were thought to increase the catalyst solubility or stability and/or prevent aggregation of the metal, but their exact role was not established unequivocally.

Finally in 2001, two research groups achieved important breakthroughs[13] with the discovery of versatile and very efficient new copper/ligand systems for the formation of C−C, C−N, and C−O bonds that enabled the use of only catalytic amounts of metal under much milder conditions (90–110 °C). These important discoveries, with their promise of being able to use a catalytic amount of copper in place of the more toxic and expensive palladium, have led to a spectacular resurgence of interest in Ullmann-type reactions. The challenge was on to devise even more effective synthetic procedures. Many research groups have been involved in the development of more efficient copper/ligand combinations to widen the scope of such reactions in terms of substrate tolerance, copper loading, milder reaction conditions, enhanced chemoselectivity, and enantioselectivity.[14] The progress has been so spectacular that, in numerous cases, the use of copper systems is now a serious rival for the alternative palladium-catalyzed procedures.

This Minireview highlights developments since 2004 in regard to the design and use of simple, easily handled supporting ligands to enhance the reactivity and selectivity of copper catalysts in intermolecular arylations of N, O, and C nucleophiles derived from aromatic and vinyl halides (Figure 1).[15,16]

The first part of the Minireview describes Ullmann coupling under homogeneous conditions, with copper-catalyzed N-arylations and N-vinylations of unsaturated N-heterocycles, amines, and amides presented first. The O-arylation and O-vinylation of phenol derivatives and aliphatic

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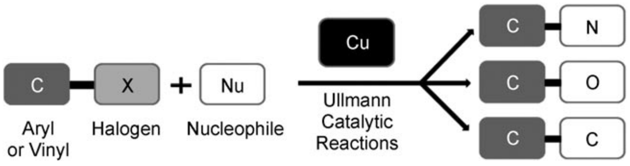


Figure 1. Scope of this Minireview.

alcohols and finally the C-arylation of active methylene compounds, cyanide ions, and alkynes (palladium-free Sonogashira-type reactions) are then discussed in succession. The second part focuses on similar Ullmann coupling reactions performed under heterogeneous conditions. Finally, in the third part, the few mechanistic studies that have emerged thus far are considered. Necessary breakthroughs still required to enable these reactions to compete fully with the well-established palladium-mediated procedures are proposed in the concluding section of this Minireview.

2. Ullmann Coupling under Homogeneous Conditions

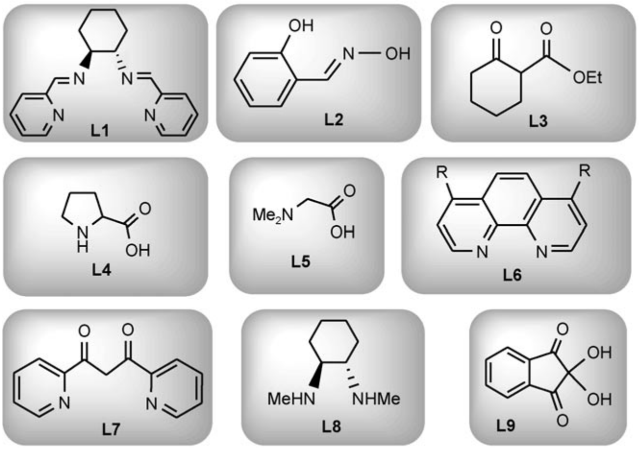
2.1. C–N Bond Formation

The copper-mediated coupling of aryl and vinyl halides to aromatic nitrogen heterocycles or amines and amides—the Ullmann[1] and the Goldberg[3] condensations, respectively—have been well-known for more than a century. By far the greatest number of reports on the modern catalytic Ullmann-type reactions have been concerned with the creation of C(sp^2)–N bonds by *ipso* substitution, and more than 150 publications have appeared since 2004. We have selected those that result in real improvement in terms of overall efficiency, taking into account parameters such as reaction temperature, catalyst loading, nature of the aryl halide (chlorides and bromides are much more demanding than iodides), and tolerance of the nitrogen nucleophiles employed. Many other efficient systems, although they can be considered as making significant contributions to the field, are outside the scope of this Minireview.[34–38]

2.1.1. Coupling Reactions of Aryl Halides with N Heterocycles

2.1.1.1. In the Presence of Supporting Ligands

Some years ago we developed polydentate ligands of the Schiff base and oxime type (such as **L1** and **L2**, respectively; Scheme 1). The use of a ligand with at least one imine group and oxygen or nitrogen coordination sites facilitates the coupling of numerous azole and amide derivatives (see Scheme 2) with aryl bromides at mild temperatures [Scheme 3, Eq. (1)].[13a,17] Some reactions with aryl iodides were even performed at 25 °C, and a turnover of about 1500 was possible in the presence of pyrazole at 80 °C.[13a,17] This application is one of the rare examples to have already been adopted industrially.



Scheme 1. Ligands for the coupling of aryl bromides and iodides to nitrogen heterocycles.

Another effective catalytic system was recently developed by Lv and Bao, who used the β-ketoester ligand **L3** [Scheme 3, Eq. (2)].[18] The coupling of different aromatic N heterocycles could be performed at mild temperatures, and reactions of aryl iodides with pyrrolidinone (Scheme 2, **S1q**) could even be conducted at room temperature.

Ma and co-workers showed that amino acids were excellent bidentate ligands for copper-catalyzed Ullmann-type reactions.[19] L-proline (**L4**) and *N*,*N*-dimethylglycine (**L5**) were particularly effective and led to the successful

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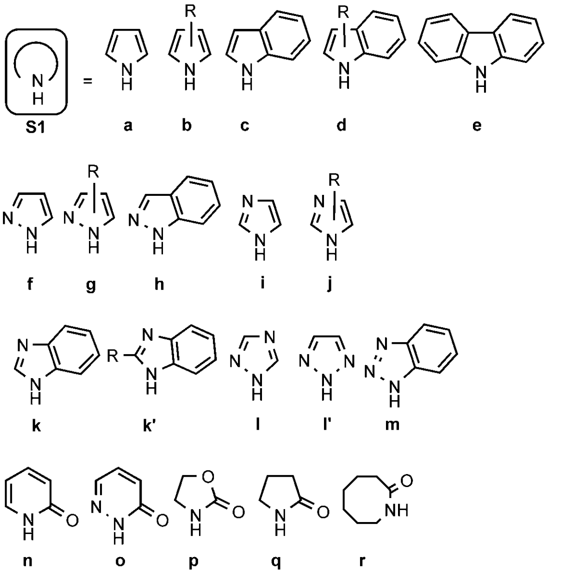
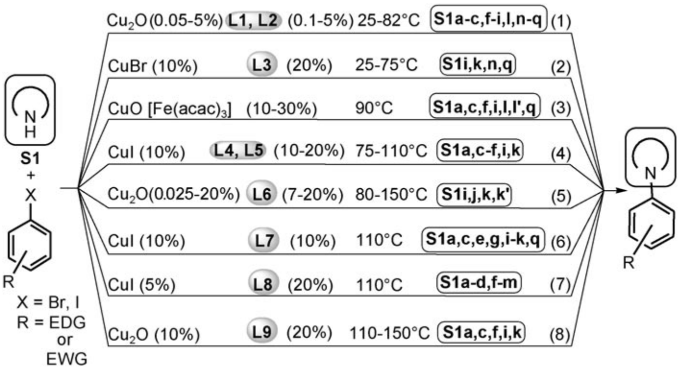


Scheme 2. Aromatic nitrogen heterocycles (**S1 a**–**m**) and cyclic amides (**S1 n**–**r**) used.



Scheme 3. Systems for the generation of C–N bonds, and the products obtained. EDG = electron-donating group, EWG = electron-withdrawing group, acac = acetyl acetonate.

coupling of numerous aryl bromides with various azoles, often at mild temperatures [Scheme 3, Eq. (4)]. The low cost of naturally occurring amino acids and their ready availability give this system real economic advantages.

Chen and co-workers reported that 1,3-diketone **L7** combined with CuI is an efficient catalytic system for the coupling of aryl bromides with nitrogen heterocycles [Scheme 3, Eq. (6)].[20] Although the reaction conditions are harsher than in the previous examples, some interesting results for the arylation of imidazole by activated chloropyridine derivatives were obtained.

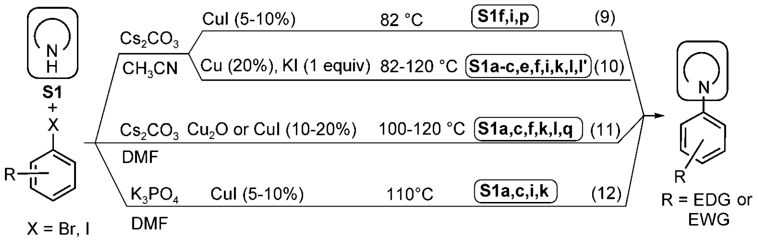
In a 2004 update[21] of an earlier study,[22] Buchwald and co-workers demonstrated the high efficiency of 1,2-diamine ligand **L8** for the coupling of aryl bromides with various types of nitrogen nucleophiles [Scheme 3, Eq. (7)]. More recently, the same research group also developed a copper/4,7-dimethoxy-1,10-phenanthroline (**L6**, R = OMe) system[23] [Scheme 3, Eq. (5)] which allows the N-arylation of a wide range of imidazole derivatives, for which no generally useful palladium-based catalysts have been reported. The use of poly(ethylene glycol) (PEG) as a solid–liquid phase-transfer catalyst and a 2000 times turnover achieved at 110 °C in one case are additional features of this system.

Xu and co-workers reported in 2008 a system based on the use of commercial ninhydrin (**L9**) as the ligand and, although the performance is poorer than the systems mentioned previously (most of the cases concern pyrazole), interestingly, unactivated chlorobenzenes take part in the reactions [albeit at the relatively high temperature of 150 °C and with modest yields; Scheme 3, Eq. (8)].[24]

The last example to be discussed relates to a system based on the condensation of numerous nitrogen heterocycles with various aryl bromides at 90 °C in the presence of the iron–copper cooperative catalyst CuO-[Fe(acac)$_3$] [Scheme 3, Eq. (3)].[25] This represents a very economically competitive alternative to the usual copper/ligand combination, and an encouraging example involving the coupling of an activated chloride has been reported.

2.1.1.2. Alternative "Ligand-Free" Conditions

Recently, several "ligand-free" systems have emerged for the N-arylation of aromatic N heterocycles catalyzed by copper compounds. The earliest preliminary results were reported in a 2005 patent [Scheme 4, Eq. (9)].[26a] Arylation using iodo- and bromobenzene was performed under "ligand-free" conditions with 5–10 % of a copper source such as CuI in the presence of Cs_2CO_3 as a base in CH_3CN. A similar system was reported three years later by Hu and co-workers, but 20 % of the copper source was used in addition to one equivalent of KI for aryl bromides to permit Br/I exchange [Scheme 4, Eq. (10)].[27] Bolm et al.[28] and Yasutsugu and Mayumi[26b] also proposed a "ligand-free-like" system in which 10 % Cu_2O (for ArI and ArBr) or CuI (for ArI) were used in DMF [Scheme 4, Eq. (11)]. In a similar system, Guo and co-workers[29] used K_3PO_4 as a base, and postulated that the phosphate group could also chelate Cu^I ions and thus



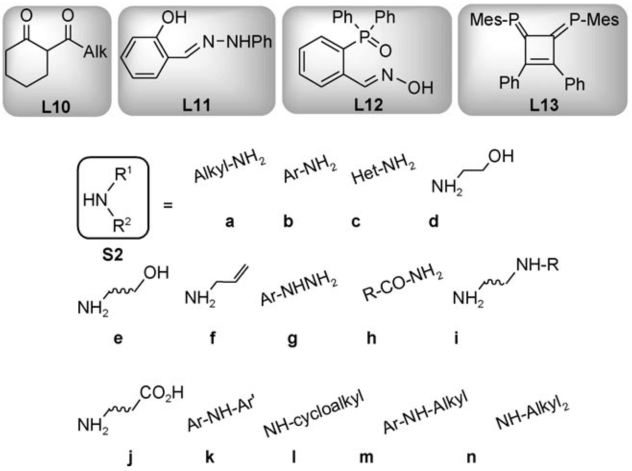
Scheme 4. Selected examples of "ligand-free-like" catalytic systems.

facilitate oxidative addition to the copper center, a proposal already made by Choudary et al. [Scheme 4, Eq. (12)].[98a]

It seems likely that the solvent and/or base acts as ligands for the copper center in all the "ligand-free" systems, although with less efficiency than the chelating organic ligands discussed earlier. Our experience has shown us that under our conditions (aromatic bromide substrates, 10% copper loading at 82 °C) a good performance is not always reproducible for ligand-free systems when the reactions are conducted on an industrial scale. The reproducibility can be improved by using a copper loading [Cu] of 20% and/or higher temperatures, but reactions conducted on an industrial scale under such conditions are questionable in regard to residual toxicity, and are more expensive. This highlights the fact—often overlooked—that supporting ligands not only accelerate the reactions but also make them more reproducible and inherently safer in terms of the operating conditions and residual toxicity.

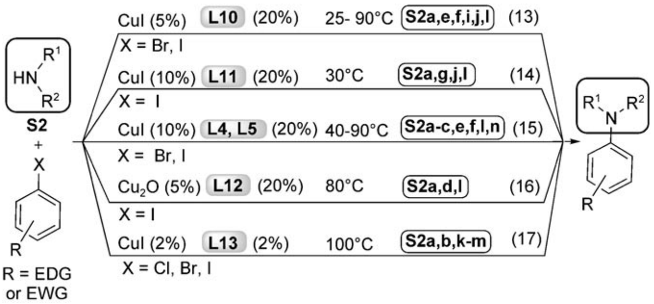
2.1.2. Coupling Reactions of Aryl Halides with Alkyl Amines, Amides, and Anilines

Recent progress in modern catalytic Ullmann coupling reactions has also led to the emergence of numerous methods to condense aryl halides (mainly iodides and bromides) with aliphatic amines, amino alcohols, hydrazines, amides, anilines, and other derivatives (Scheme 5).



Scheme 5. Ligands used and the range of N substrates that can be used in the copper-catalyzed coupling with aryl halides.

In 2006, one of the first examples of a room-temperature Ullmann condensation was reported by Buchwald and co-workers [Scheme 6, Eq. (13)].[30,50] The use of 1,3-diketone **L10** (Alk = *i*Pr) in combination with CuI (5%) enabled the condensation of aryl iodides with primary or secondary alkyl amines[30] as well as amino alcohols[50] to be performed in excellent yields at 25 °C. This system, based on the inexpensive ligand **L10** (Alk = *i*Pr) is also efficient under harsher conditions (90 °C) with aryl bromides. It nicely complements the related palladium-based methods for the N-arylation of aliphatic amines.



Scheme 6. Selected examples of copper/ligand systems for the formation of C–N bonds.

In a similar fashion, Fu and co-workers published two interesting room-temperature systems based on *rac*-1,1′-bi-2-naphthyl (*rac*-binol) and *N*-phenylhydrazone **L11** ligands [Scheme 6, Eq. (14)].[31] These ligands in association with 10% CuI or CuBr resulted in high reactivities for the N-arylation of aliphatic amines and/or amino acids with aryl iodides.

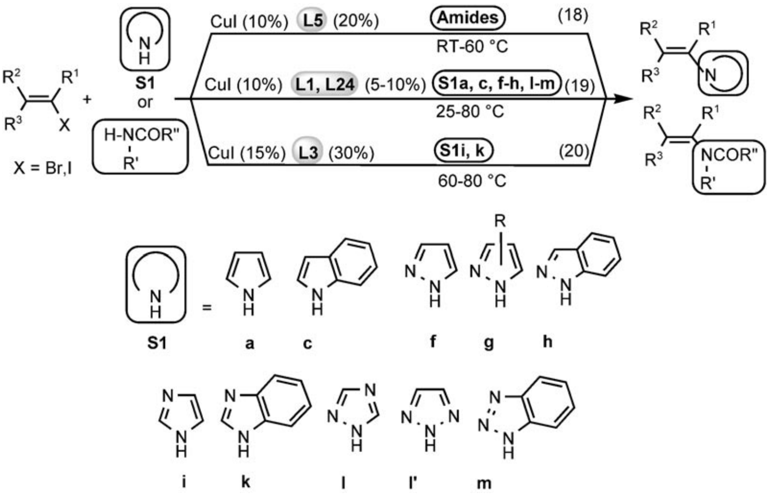
In 2005 Ma and co-workers showed that the amino acid L-proline (**L4**) and glycine derivative **L5** are highly efficient ligands with CuI for the coupling of alkyl amines and aniline derivatives over a temperature range of 40 to 90 °C [Scheme 6, Eq. (15)]. These ligands, which probably chelate the copper ion through the carboxy and amino groups, could make the catalytic Cu^I species more reactive toward an eventual first oxidative addition or coordination of the aryl halide.[19c]

Phosphine-oxime **L12** also proved to be a good ligand for the N-arylation of alkylamines and N heterocycles by aryl iodides [Scheme 6, Eq. (16)].[32] Although product formation takes place at higher temperatures (80 °C) than in other cited examples, the replacement of N by P in ligand **L12** constitutes an interesting feature for mechanistic studies.

The last system selected for discussion, developed in 2005 by Yoshifuji and co-workers, also involves a phosphorus-containing ligand **L13**.[33] Although the ligand is rather complex, it enables the remarkable coupling of aniline and morpholine with non-activated aryl chlorides at a moderate temperature [Scheme 6, Eq. (17)].

2.1.3. Coupling Reactions of Vinyl Halides with N Nucleophiles

Ligand-assisted copper catalysis recently led to the development of modern versions of the Ullmann and Goldberg reactions of vinyl halides.[38] Ma and co-workers demonstrated that they could generate a wide array of enamides under mild conditions by using amino acid **L5** [Scheme 7, Eq. (18)].[38b] Porco and co-workers reported the copper/phenanthroline(**L17**)-mediated coupling of amides with β-iodo-acrylates and acrylamides to prepare N-acyl vinylogous carbamates and ureas.[38c] Our research group also showed that the synthesis of various *N*-vinylazoles occurs very efficiently in the presence of CuI and **L1**[58] or **L24**[95] [Scheme 7, Eq. (19); see **L24** in Scheme 17]. Finally, Bao et al. were able to couple pyrazole and indazole with vinyl halides (X = Br, I) at 60–80 °C in the presence of β-diketone **L3** [Scheme 7, Eq. (20)].[38l]



Scheme 7. Selected examples of copper/ligand systems for the formation of C–N bonds.

2.2. C–O Bond Formation

The synthesis of diaryl ethers and related derivatives by classic Ullmann methods has been well-known for a long time.[2] Despite the recent renaissance of the catalytic Ullmann method, fewer publications have appeared for C–O than for the related C–N coupling reactions, but the total since 2004 is still more than 50. The same criteria for selecting studies to include in the discussion were applied as in the previous section.

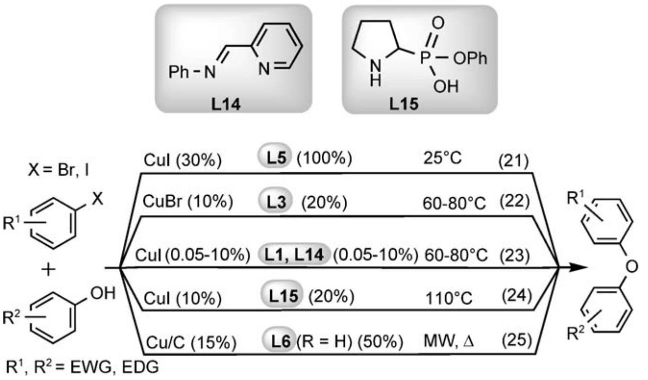
2.2.1. Coupling Reactions of Aryl Halides with Phenols

Ma et al., after further development of a system reported earlier,[39] described an efficient catalytic C–O coupling reaction at ambient temperature.[40] Thus, by using the amino acid **L5** as a supporting ligand with 30 % copper loading, they could couple 2-bromotrifluoroacetanilide and L-tyrosine derivatives in high yields at 25 °C [Scheme 8, Eq. (21)].

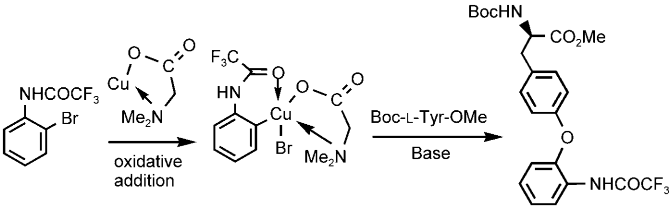
A particular advantage of the ambient-temperature conditions used with this system is that the coupling can occur without any accompanying racemization of the tyrosine derivatives. A drawback to this procedure remains the rather high copper and ligand loadings. It also appears that an *ortho*-amide substituent on the aryl halide is required as a directing group. The additional stabilization of the Cu^I center provided by O coordination of this chelating *ortho* group was proposed to be a key factor for the success of these reactions (Scheme 9).

The catalytic system of Lv and Bao described above for the formation of C–N bonds is also efficient for the copper-catalyzed arylation of phenol derivatives. The use of the same β-keto ester **L3** as a supporting ligand affords the corresponding diaryl ethers from aryl bromides at mild temperatures [Scheme 8, Eq. (22)].[18]

Similarly, the Schiff bases **L1** and **L2**, which we developed for other types of coupling reactions, as well as ligand **L14**, are also very efficient at promoting the synthesis of diaryl ethers [Scheme 8, Eq. (23)].[13a,41] In combination with 10 % CuI and the inexpensive base K_3PO_4 these ligands allow the coupling of a large range of aryl bromides with phenols under mild conditions. It is worth noting that very low copper and ligand loadings are apparently able to promote some of these reactions (see chapter 4, Scheme 32).[41b,d]



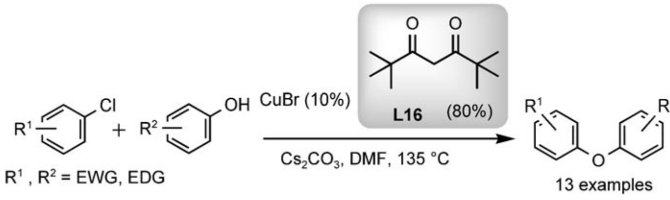
Scheme 8. Selected systems for the generation of diaryl ethers from ArI or ArBr.



Scheme 9. *Ortho* chelating effect for the room-temperature arylation of *N*-Boc-L-tyrosine without racemization. Boc = *tert*-butoxycarbonyl.

The coupling of phenols with aryl iodides or bromides is also possible with pyrrolidine-2-phosphonic acid phenyl monoester (**L15**) at higher temperatures [Scheme 8, Eq. (24)],[42] or with 1,10-phenanthroline as the supporting ligand (**L6**, R = H). The latter was used in association with a KF/Al_2O_3 system as the base[43] or in the presence of copper impregnated into charcoal under microwave irradiation [Scheme 8, Eq. (25)].[44]

Another significant advance was achieved in our research group with the development of an efficient method for the copper-catalyzed arylation of phenols by aryl chlorides (Scheme 10).[45] This system, based on the use of the ligand 2,2,6,6-tetramethyl-3,5-heptadione (**L16**), is to our knowledge the first one able to condense both activated and deactivated aryl chlorides. Although relatively harsh conditions are used (135 °C), this procedure has real economic advantages in that very inexpensive materials are used.



Scheme 10. Copper-catalyzed arylation of phenols by aryl chlorides.

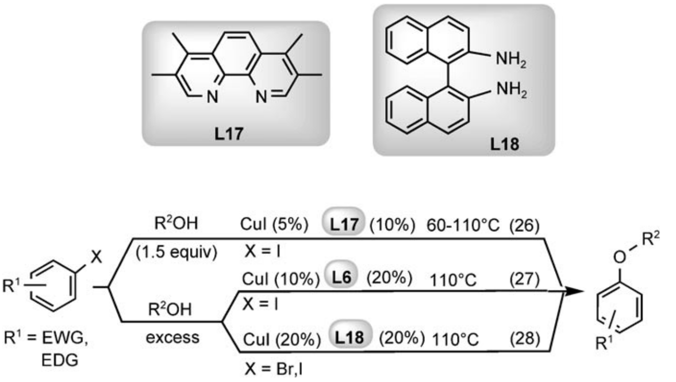
As in the case of C–N coupling, some reports have appeared in the literature for "ligand-free" methods. We showed in 2004 that the arylation of phenols by aryl iodides was possible in acetonitrile at 82 °C by using a copper precursor without additional supporting ligands.[26a] Two others examples were recently reported,[46,47] but very high reaction temperatures are needed (150–160 °C) since aryl iodides and bromides are employed.

Many other studies on the formation of C(Ar)–O(phenol) bonds by using ligand-assisted methods are not discussed as they are outside the scope of this Minireview.[48]

2.2.2. Coupling Reactions of Aryl Halides with Alcohol Derivatives

There are only a few known catalytic copper systems that facilitate the coupling of aryl halides with aliphatic alcohols. In 2008, the Buchwald research group, in a comprehensive study of an earlier system,[49,50] used a highly efficient phenanthroline ligand **L17**, which enables this reaction to be carried out with aryl iodides under mild conditions.[51] Their method is particularly noteworthy for not needing a large excess of alcohol and for being remarkably selective for O-arylation when amino alcohols are involved [Scheme 11, Eq. (26)].

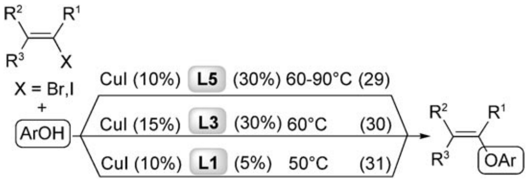
The coupling of alcohols with aryl iodides has also been realized by Hosseinzadeh et al., who used phenanthroline (**L6**, R = H) or its derivatives as the ligand[43] with KF/Al_2O_3 as the base (in the presence of a large excess of phenol), and by Evano and co-workers in the first total synthesis of paliurine F (a sedative).[52] Amino acids[53] and also the 1,1′-binaphthyl-2,2′-diamine (binam) ligand **L18**[54] give interesting results, but here the problem of having the nucleophile (the alcohol) in excess remains [Scheme 11, Eqs. (27) and (28)].[55]



Scheme 11. Selected efficient systems for the generation of alkyl aryl ethers.

2.2.3. Coupling Reactions of Vinyl Halides with Phenol Derivatives

The coupling of vinyl halides with phenol derivatives is also possible by Ullmann-type reactions. The corresponding vinyl aryl ethers are an important class of building blocks in organic synthesis as well as synthetic targets for the polymer and life science industries. However, this methodology has not been developed nearly as much as the variant using aryl halides. Since 2004, Ma et al.,[56] Bao et al.,[57] and our research group[58] [Scheme 12, Eqs. (29)–(31), respectively)] have observed that some of the systems presented above for arylation by aromatic halides are also very efficient with vinyl halide substrates (the reaction is often facile). These procedures, which take place under very mild temperatures, have been applied (in the presence of the phenanthroline ligand) for the total synthesis of abyssenine A, a compound which displays considerable biological activity.[59]



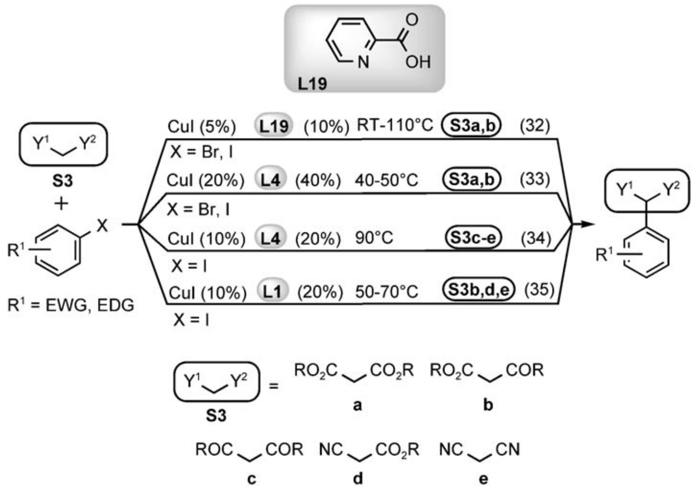
Scheme 12. Efficient systems for the generation of aryl vinyl ethers.

2.3. C–C Bond Formation

2.3.1. Ullmann–Hurtley Condensations

In a recent report, Kwong and co-workers described a mild catalytic system which allows the arylation of diethyl malonate by a wide range of aryl iodides at 25 °C in the presence of 2-picolinic acid (**L19**) as the supporting ligand [Scheme 13, Eq. (32)].[60] A higher temperature is needed (70 °C) for reactions with other 1,3-dicarbonyl derivatives (dimethyl malonate, β-ketoesters), and an even higher one when the reaction is performed with aryl bromides (110 °C).

L-Proline (**L4**) also appears to be an excellent ligand for this reaction, as reported by Ma and co-workers.[61] Con-

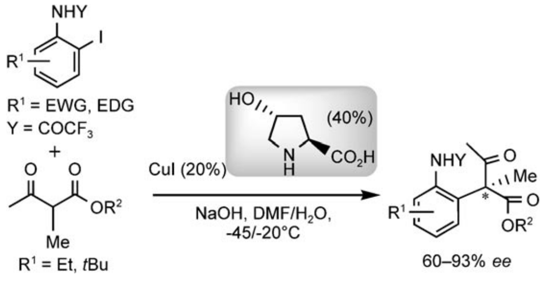


Scheme 13. Arylation of activated methylene compounds.

densations of aryl halides (ArI and ArBr) with activated methylene compounds (dialkyl malonate and β-ketoesters) are performed at 40–50 °C [Scheme 13, Eq. (33)]. Jiang et al. reported a very similar system, but it is restricted to expensive aryl iodides and a higher temperature (90 °C) for the arylation of β-diketone, ethyl cyanoacetate, or malonitrile [Scheme 11, Eq. (34)].[62]

A year earlier we presented a general method for the arylation of several malonic acid derivatives by aryl iodides [Scheme 13, Eq. (35)].[17a] The use of the Schiff base **L1** as the ligand allowed the reactions to be performed under very mild conditions (50–70 °C) in the presence of molecular sieves.

The first enantioselective Ullmann–Hurtley condensation was reported in 2006 by Ma and co-workers.[63] They described the CuI-catalyzed asymmetric coupling (at −20/−45 °C) of various 2-iodotrifluoroacetanilides with 2-methyl acetoacetates by using (2*S*,4*R*)-4-hydroxyproline as the supporting ligand and chiral source (Scheme 14). Although the application of this method is limited by the necessary presence of chelating substituents in the *ortho* position, this method undoubtedly represents an interesting advance in terms of the enantioselectivity.[14]



Scheme 14. Copper-catalyzed asymmetric coupling of 2-iodotrifluoroacetanilides with 2-methyl acetoacetates.

The application of the same system to the arylation of non-carbon-substituted β-keto esters leads to a simple and convenient method for preparing a wide range of 2-(trifluoromethyl)indoles.[64] It is also noteworthy that in the presence of a very large excess of ethyl acetoacetate (this β-ketoester probably also plays the role of supporting ligand) the copper-catalyzed arylation leads to the deacylated product. This interesting result suffers, however, from poor chemoselectivity (formation of arylated acetoacetate).[65] Proline (**L4**) was also used in the only example reported for the copper-catalyzed functionalization of activated methylene compounds by vinyl halides ((2-bromovinyl)benzenes).[66]

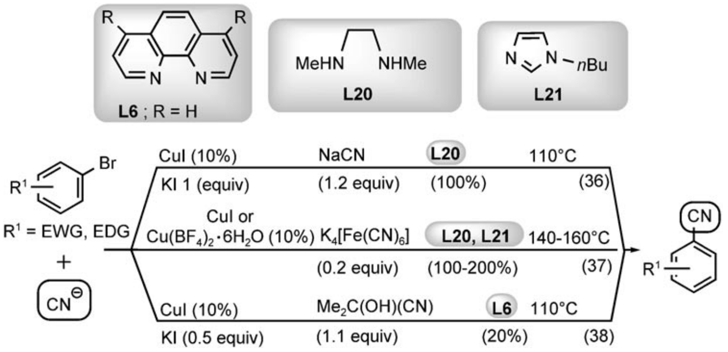
2.3.2. Cyanation Reactions

The direct reaction between aryl halides and cyanide sources to afford aryl nitriles has been well known for 80 years as the Rosenmund–von Braun reaction.[67] This reaction, however, suffers from the same major drawbacks that afflict other Ullmann-type copper-coupling reactions. Surprisingly, very few reports have described really efficient procedures that can be performed under mild catalytic conditions in the presence of supporting ligands (Scheme 15).

Some years ago, the Buchwald research group reported a copper-catalyzed "domino" halogen-exchange/cyanation procedure for aryl and heteroaryl bromides [Scheme 15, Eq. (36)].[68] Although the authors made use of the 1,2-diamine **L20**, a disadvantage of their approach is the use of highly toxic NaCN; furthermore the reactions are performed at 110–130 °C and require stoichiometric quantities of ligand. Another method, also based on a Finkelstein-type reaction, was developed in which 1,10-phenanthroline (**L6**, R = H) is used as a ligand [Scheme 15, Eq. (38)].[69] This copper-assisted cyanation of aryl bromides occurs at 110 °C through the in situ copper-catalyzed production of aryl iodides in the presence of catalytic amounts of KI. The advantages of this protocol include the use of a catalytic amount of ligand and the less-toxic, easily handled liquid acetone cyanohydrin as the cyanating agent.[70] More recently, an even safer alternative was reported by Beller and co-workers, who showed that the copper-catalyzed cyanation of aryl bromides is efficient [Scheme 15, Eq. (37)] when the nontoxic cyanide source $K_4[Fe(CN)_6]$ is used in the presence of ligands of the 1-alkylimidazole type (for example, **L21**).[71] A drawback to this procedure is the very high temperatures (140–160 °C) required and the need to use two equivalents of ligand. A variation of this method, also based on halide exchange (using KI) and employing ligand **L20** was reported by the same research group.[72]

2.3.3. Sonogashira-Type Reaction: Coupling of Aryl Halides with Terminal Acetylenes

A useful method to prepare aryl alkynes is the Sonogashira reaction,[73] which corresponds to a Pd/Cu co-catalyzed coupling reaction between aryl halides and terminal acetylenes.[74] Since the pioneering studies on palladium-free catalyzed Sonogashira coupling reactions were described by Miura and co-workers in 1993 (which correspond to a catalytic version of the Stephens–Castro reaction[75]),[76] few examples exploiting the method have been reported, mainly because the competing Glaser reaction (homocoupling of

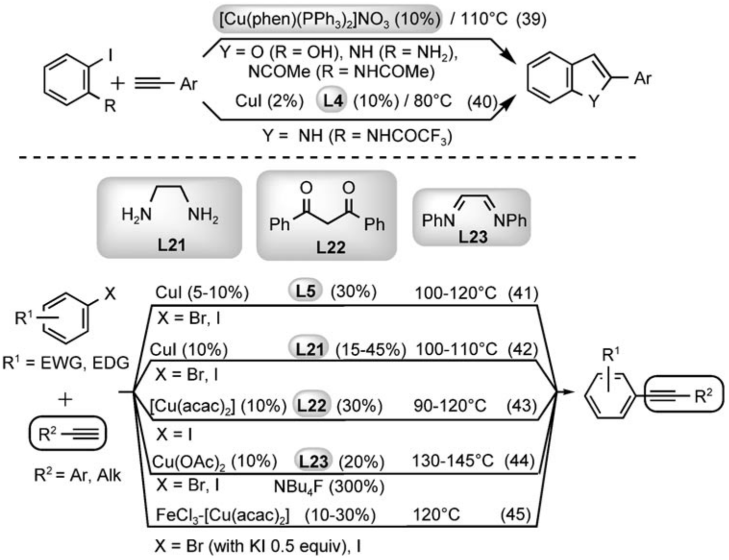


Scheme 15. Copper-catalyzed cyanation of aryl halides.

terminal acetylenes catalyzed by copper salts) is difficult to avoid.[77]

In a 2005 extension of an earlier study,[78] Venkataraman and co-workers demonstrated the high efficiency of the well-defined catalytic precursor $[Cu(phen)(PPh_3)_2]NO_3$ (phen = phenanthroline) for the coupling of aryl iodides with terminal acetylenes [Scheme 16, Eq. (39)].[79] It is worth noting that, in contrast to palladium-based protocols, the reaction is possible with functional groups at the *ortho* position, thereby allowing the elegant in situ synthesis of various cyclic compounds (benzofurans and indoles). This strategy, first described by Cacchi et al.,[80] was also employed more recently in the presence of proline (**L4**) by Ma et al. [Scheme 16, Eq. (40)].[81]

In 2004, Ma and Liu reported a copper/amino acid (**L5**) system for the coupling of both ArI and ArBr compounds with alkyl and aryl acetylenes.[82] This reaction [Scheme 16, Eq. (41)] tolerates substituted aryl acetylenes, alkyl acetylenes, and even propargylic ethers. Another good catalytic system for this coupling was developed by Guo and co-workers,[83] who used diamine **L21** as the ligand [Scheme 16, Eq. (42)]. Excellent yields were achieved for the coupling of aryl iodides with phenylacetylene and 1-octyne, but in contrast aryl bromides gave modest yields (44–71 %). Our research group has also developed a catalytic system based on $[Cu(acac)_2]$ and dibenzoylmethane (**L22**) as the ligand [Scheme 16, Eq. (43)].[84] This easily handled and inexpensive system is applicable to the coupling of a wide range of activated and deactivated aryl iodides with aryl and alkyl acetylenes. Interestingly, the co-catalytic iron–copper system described above for the C–N coupling[25] also allows the condensation of phenylacetylene with aryl iodides or aryl bromides (in the presence of NaI for the later) [Scheme 16, Eq. (45)].[25a] The diazabutadiene **L23** is also a suitable supporting ligand for this type of reaction,[85] but relatively high temperatures (130–145 °C) are necessary to form diaryl and alkyl aryl acetylenes from aryl iodides and activated aryl bromides [Scheme 16, Eq. (44)]. The interesting features of this system are the possibility of working under aerobic and solvent-free conditions. In 2004 He and Wu described an alternative approach in which copper-mediated Sonogashira-type coupling is effected by using microwave heating.[86] More recently, Lamaty and co-workers also used this technique with



Scheme 16. Selected examples of Pd-free Sonogashira-type coupling.

poly(ethylene glycol) (PEG) as the solvent (and probably as a ligand for the copper).[87] Although excessive temperatures (190–220 °C) are used, both methods interestingly require only very short reaction times (30 min–2 h). It is also noteworthy that a palladium-free copper-catalyzed version of the Sonogashira coupling was developed for the synthesis of 1,3-enynes. Venkatamaran and co-workers[79,88] and Liu and Ma[81] used the well-defined complex $[Cu(bipy)PPh_3Br]$ (bipy = 2,2-bipyridine) and CuI/**L5**, respectively, as catalyst (10 %) systems to couple vinyl iodides and terminal acetylenes under mild reaction conditions. An interesting example of a coupling reaction performed in the absence of a ligand (with 20 % copper) was also reported by Shao and Shi.[89] These procedures substantially increase the potential for copper-mediated C–C bond formation.[90]

3. Reusable Catalysts for Ullmann Coupling under Heterogeneous Conditions

Numerous methods have been developed for conducting palladium-mediated cross-coupling reactions with supported catalysts.[91] Such is not the case for catalytic Ullmann reactions, which suffer from a lack of recyclable and reusable systems. Of the few that have been developed, most are suitable only for C–N coupling reactions, and very few have been developed for the formation of C–O and C–C coupling bonds.[92]

3.1. Heteregeneous Cu Systems for C–N Bond Formation

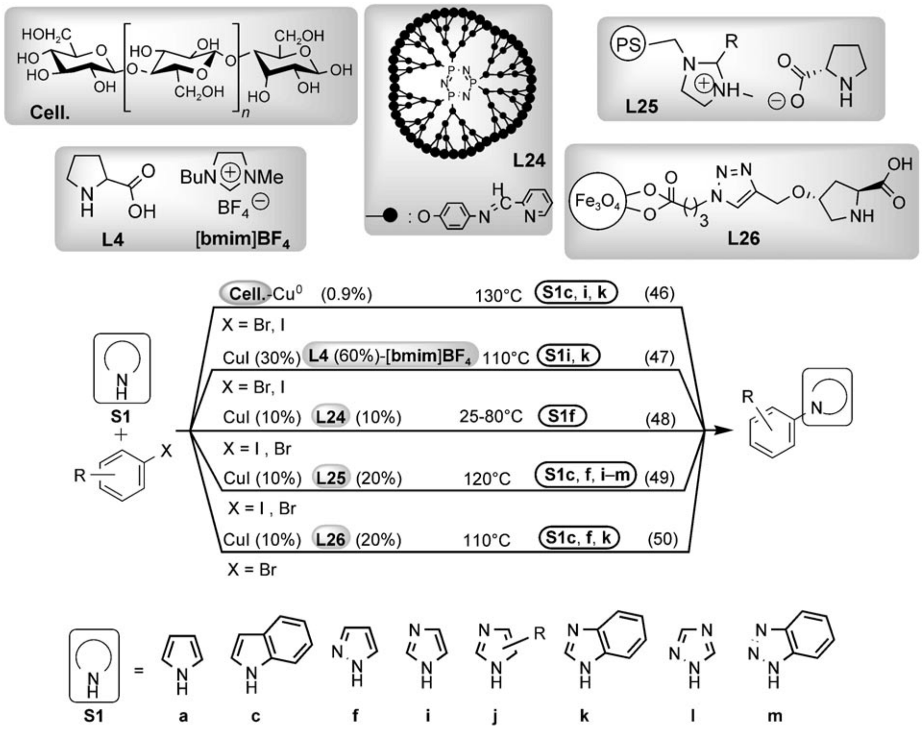
Various sorts of supports have been designed specifically for the condensation of unsaturated N heterocycles (**S1 a**,**c**,**f**,**i**–**m**) with aryl halides (Scheme 17).

One interesting example was published by Kantam, Reddy, and co-workers,[93] in which they reported the N-arylation of nitrogen heterocycles with ArI and ArBr catalyzed by cellulose-supported copper(0) in the absence of any external ligands [Scheme 17, Eq. (46)]. A high temperature is used, but the catalyst can easily be reused four times with an average leaching of 0.8 % of the copper (note that such crucial information is rarely given in the literature).

Bao and co-workers showed that room-temperature ionic liquids based on imidazolidinium derivatives such as $[Bmim]BF_4$ enable copper-catalyzed condensations to be carried out between imidazole derivatives and aryl bromides at 110 °C.[94] The catalyst can be recovered in the presence of proline ligand (**L4**, 60 %) by extraction with low-polarity solvents, and is still efficient after four runs, although with decreased yields [Scheme 17, Eq. (47)].

Heterogeneous system **L24** (an iminopyridine ligand grafted onto phosphorus dendrimers) reported by Majoral and co-workers is a very gentle catalyst.[95] A spectacular dendritic effect, rare in the field of organometallic chemistry, is observed, which allows the coupling of aryl iodides or vinyl bromides with pyrazole at 25–80 °C [Scheme 17, Eq. (48)]. The stability of the support enables this system to be reused.

You and co-workers have described an original concept in which supported amino acid ionic liquids **L25** coupled with CuI effect the N-arylation of nitrogen heterocycles with aryl bromides or activated aryl chlorides [Scheme 17, Eq. (49)].[96]



Scheme 17. Reusable systems for the coupling of nitrogen heterocycles with aryl halides.

This recoverable system is still efficient after nine runs (yield: 73%) for the coupling of activated 4-bromobenzonitrile and imidazole. However, it presents several drawbacks such as the synthetic complexity of the ligand and the long reaction times required (60 h).

Alper and co-workers developed a system based on a proline ligand supported on magnetic nanoparticles (**L26**).[97] The arylation of nitrogen nucleophiles by (hetero)aryl bromides occurs in the presence of CuI. A unique feature of this system is that an external magnet can hold the ligand in place while the substrates are decanted. In this way, the ligand can be successfully reused four times for the coupling of activated 4-bromoacetophenone with imidazole [Scheme 17, Eq. (50)].

Copper fluoroapatite (Cu-**FAP**) is a supported catalytic system which shows remarkable activity for the coupling of aryl chlorides and even activated aryl fluorides with several N nucleophiles [Scheme 18, Eq. (51)].[98] This reusable system is thought to function through the strong basicity of the apatite support, thus enabling the metal to activate C(Ar)−Cl or C(Ar)−F bonds. Choudary et al. performed an interesting series of experiments, on the basis of which they proposed that the nucleophilic substitution of the N heterocycle takes place before activation of the haloarene occurs (see Section 4).

A system has been reported by Punniyamurthy et al. in which copper nanoparticles are used [**Cu nano**, Scheme 18, Eq. (52)].[99] This inexpensive catalyst, which operates in air under ligand-free conditions, enables the condensation of various aryl iodides with N nucleophiles. **Cu nano** is reusable, and has good activity after three sequential coupling reactions of aniline with PhI. It is also worth noting that an acceptable yield (60%) is obtained for the coupling of $PhNH_2$ with the demanding substrate PhCl.

Cu_2O-coated Cu nanoparticles (Cu_2O/Cu) had previously been used by Hyeon and co-workers in 2004 for the coupling (at 150 °C in DMSO) of nitrogen nucleophiles with aryl chlorides activated by electron-withdrawing substituents [Scheme 18, Eq. (53)]. Nothing was reported concerning the reusability of this system.[100]

The silica-tethered copper complex Cu-**L27** has been used as a catalyst for the arylation of nitrogen heterocycles with aryl iodides and some activated aryl bromides [Scheme 18, Eq. (54)].[101a] This system, based on supported iminopyridine ligands, can be reused several times. A low copper leaching rate of 2.5%, expressed as the percentage of the total copper charge, was observed.

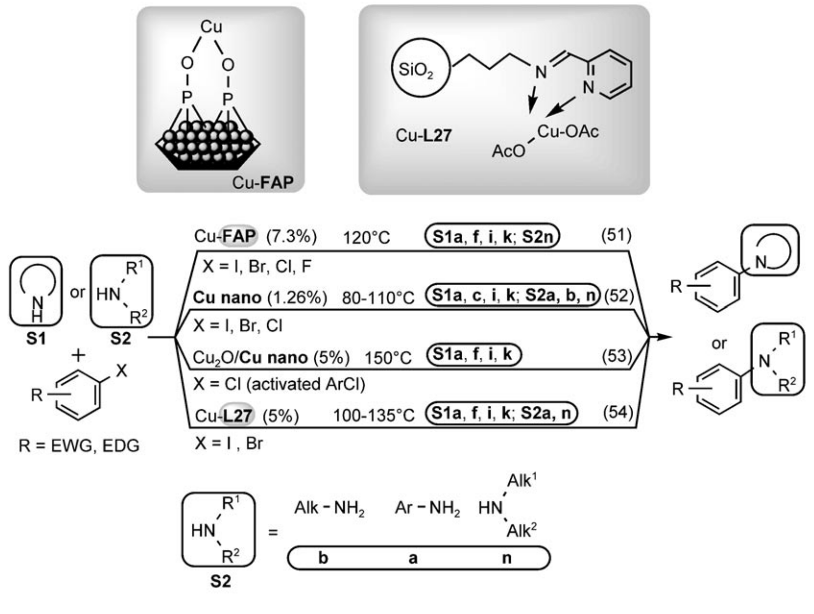
3.2. Heteregeneous Copper Systems for the Formation of C−O Bonds

Only a few efficient, recyclable, catalytic systems for the condensation of aryl halides with various phenols have been reported (Scheme 19).

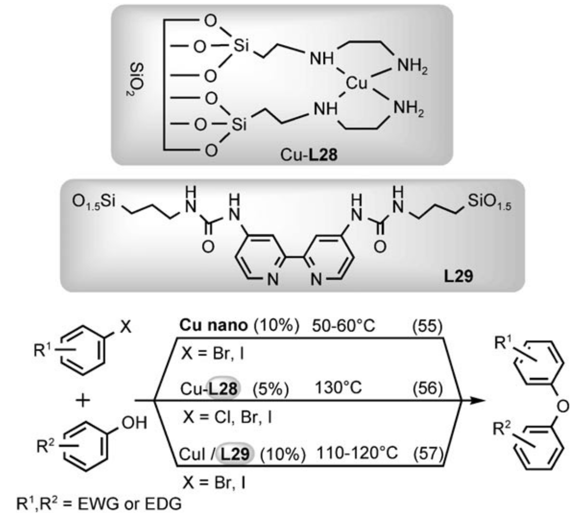
A mild heterogeneous system (50–60 °C) based on copper nanoparticles (**Cu nano** (18 nm), 10%) for the coupling of aryl iodides and aryl bromides with phenols was developed by Kidwai et al. [Scheme 19, Eq. (55)]. The reactions take place without any added ligand and the system is reusable, although a decrease in yield is observed and a longer time reaction is required for each subsequent run.[102]

Recently, Mao and Wang[103] reported that a diamine-type ligand, anchored to silica and chelated to copper, efficiently promotes the synthesis of diaryl ethers from aryl iodides, aryl bromides, or even activated aryl chlorides at 130 °C [Scheme 19, Eq. (56)]. This catalytic system (Cu-**L28**) was recovered and reused 10 times for the reaction of PhOH with PhI.

In our research group we devised a sol–gel immobilized copper catalyst Cu-**L29**, and applied it for the first time to the C−O coupling of aryl iodides and aryl bromides with



Scheme 18. Heterogeneous systems for the coupling of nitrogen heterocycles and/or amines with aryl halides.



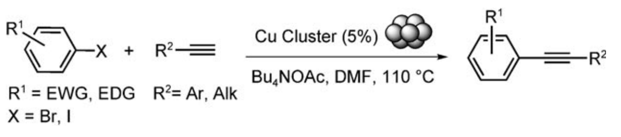
Scheme 19. Supported systems for the coupling of phenols with aryl halides.

phenols.[104] The corresponding diaryl ethers were obtained in excellent yields after ten reuses of this catalyst system [Scheme 19, Eq. (57)]. An interesting low average amount of copper leaching was measured in the solution phases containing the diaryl ethers (0.7 %, expressed as a percentage of the copper charge).

3.3. Heteregeneous Copper Systems for C–C Bond Formation

To our knowledge, only three published reports describe the use of supported copper catalysts for the formation of a C–C bond by a palladium-free Sonogashira-type reaction.

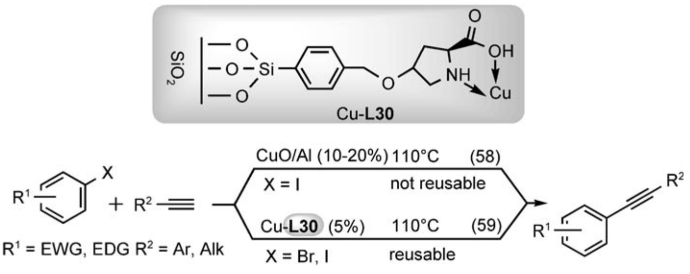
The first example was described by Rothenberg and co-workers.[105] The copper nanoclusters, prepared by reducing copper chloride precursors with tetraoctylammonium formate (TOAF), were used to couple various aryl iodides and activated aryl bromides with phenylacetylene. TOAF also acts as a stabilizer, forming an organic corona around the clusters which prevents their aggregation. The system, for which no ligands are needed, seems to be reusable (3 runs; Scheme 20)



Scheme 20. Copper nanoclusters for reusable Sonogashira coupling.

Another example reported by Biffis, Ravasio et al. deals with a heterogeneous copper catalyst on alumina (CuO/Al). Interesting reactivity for the coupling of aryl iodides with phenylacetylene was observed, but the high amount of copper leaching measured (62 %) does not permit this system to be reused [Scheme 21, Eq. (58)].[106]

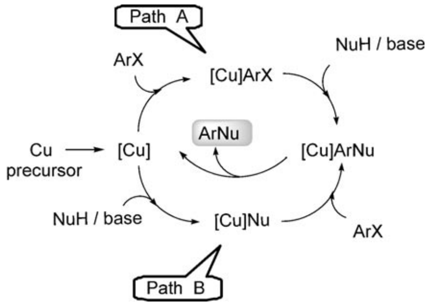
The third example is a silica-anchored proline–copper(I) complex Cu-**L30** reported by Wang et al. [Scheme 21, Eq. (59)]. This efficient reusable catalyst enables the coupling of aryl iodides and aryl bromides with various aryl and alkyl acetylenes (6 successive runs were performed using phenylacetylene and iodoanisole).[107]



Scheme 21. Supported systems for Sonogashira-type reactions.

4. Mechanism

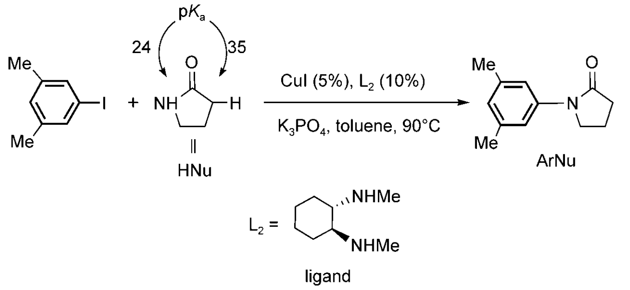
The mechanism of palladium catalysis is better understood than is that of copper catalysis. Two formal representations can be proposed for the copper-catalyzed arylation of nucleophiles. In the first, the putative oxidative addition of the aryl halide (ArX) proceeds before the nucleophilic substitution of NuH, which itself precedes the formation of the coupling product (ArNu) and regeneration of the catalytic copper species (Path A, Scheme 22). In the second proposed pathway, nucleophilic substitution occurs in the first step (Path B). As far as the oxidation state of the copper is concerned, these types of reactions are thus supposed to proceed via Cu^{I} and Cu^{III} intermediates.[5,6]



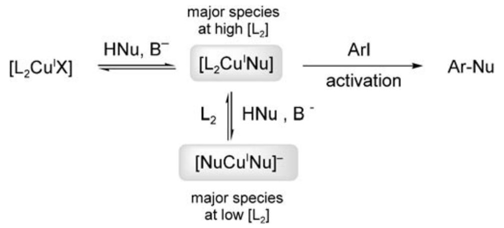
Scheme 22. Two possible pathways for the copper-catalyzed arylation of nucleophiles.

Most of the recent studies concern the mechanism of the copper-catalyzed arylation of amides and derivatives, and assume that the nucleophilic pathway “B” occurs. Thus, in 2005 Buchwald and co-workers reported a mechanistic study on the copper-catalyzed amidation of 3,5-dimethyliodobenzene promoted by a *N,N*-chelating cyclohexylene diamine ligand L_2 (L_2 is the general form of this diamine in Schemes 23, 24, 26).[108]

They proposed the generation of a copper(I) amidate $[L_2Cu^{I}Nu]$ as the active intermediate which is chemically and kinetically capable of reacting with ArI to afford the corresponding N-arylated amides (Scheme 24). Kinetic data



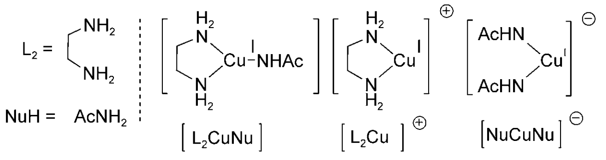
Scheme 23. Copper-catalyzed amidation of 3,5-dimethyliodobenzene.



Scheme 24. Proposed mechanism for the copper-catalyzed amidation of aryl iodides. B = base.

show that high ligand concentrations favor the formation of this intermediate and allow the activation of the aryl iodide to become the rate-limiting step. At low ligand concentrations, the formation of another copper complex $[NuCu^INu]^-$ is favored, which results from multiple coordination of the amide and is less reactive towards ArI.

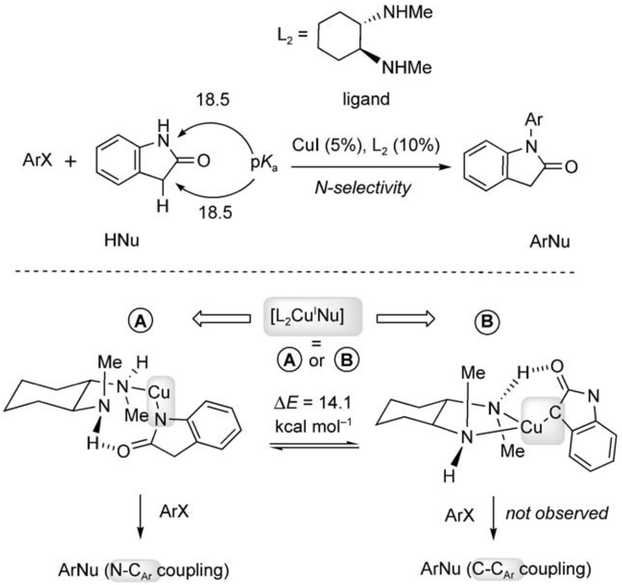
In 2007 Liu and co-workers performed a theoretical examination of a very similar reaction: the Cu^I-catalyzed coupling of PhBr with acetamide in the presence of ethylenediamine as the ligand.[109] The results obtained are fully consistent with the preferential involvement of the active $[L_2CuNu]$ intermediate proposed by Buchwald and co-workers. Other possible pathways involving the formation of, for example, cationic diamine-coordinated Cu^I or of multiple anionic amide-ligated Cu^I complexes as intermediates were discarded (Scheme 25).



Scheme 25. Possible intermediates for the copper-catalyzed amidation of aryl halides.

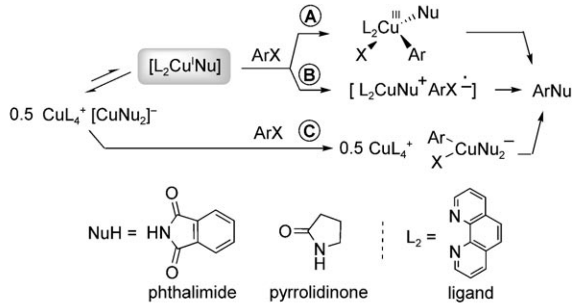
These authors also proposed that the activation of the aryl halide was the rate-limiting step. An oxidative addition would lead to the formation of pentacoordinate Cu^{III} complexes, from which a more facile reductive elimination step could occur through a square-pyramidal structure.[109]

Very recently three reports on the mechanism of the Goldberg reaction appeared simultaneously.[110–112] Buchwald and co-workers reported an efficient copper-based catalyst system that allows the selective N-arylation of oxindoles in the presence of the cyclohexylenediamine ligand (Scheme 26).[110] The identical acidities of the protons at positions C3 and N1 ($pK_a = 18.5$) means that the cross-coupling reactions of unprotected oxindole with aryl halides might also provide the C–aryl product. To gain mechanistic insight into the controlling features of the N chemoselectivity, the authors performed computational studies on four diamine-copper(oxindolate) $[L_2Cu^INu]$ species that result from the initial addition of the nucleophile to the $[L_2Cu^IX]$ precursor and potentially able to provide various regioisomeric products in the presence of ArX. These studies revealed that the intermediate **A** leading to the N–aryl product, was found to be significantly lowest in energy among the possible structures. For example, **A** is favored by 14.1 kcal mol^{-1} over isomer **B**, which may provide the C–aryl product (the later was never observed). Theoretical calculations suggest that selectivity might be governed by the rapid activation of ArX by **A** relative to **B** and/or by the fact that isomerization between these two species might not occur.



Scheme 26. Selective copper-catalyzed N-arylation of oxindoles.

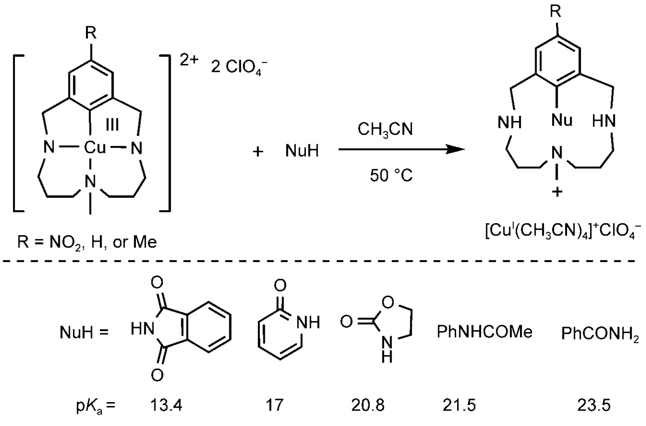
Hartwig and co-workers were able in 2008 to isolate copper(I) imidate and amidate intermediates of the $[L_2Cu^INu]$ type (in Scheme 27, L_2 is formally a chelating *N*,*N*-phenanthroline group).[111] The characterization of the amidate intermediates has shown that these can exist, depending on the conditions, in both the ionic and neutral forms. Among three potential mechanisms for this reaction, the authors discard the direct activation of the haloarene by the ionic $CuL_4{}^+CuNu_2{}^-$ form (Scheme 27, path C). The two other pathways (Scheme 27, paths A and B) involve activation of the haloarene ArX by the neutral species $[L_2Cu^INu]$. Studies on the effect of the electronic properties of ArX and on the reaction of ArI containing a radical clock argue against a mechanism initiated by electron transfer (Path B) followed by dissociation of the halide (providing $Ar^\bullet$ and X^-) from the



Scheme 27. Three potential mechanisms for the copper-catalyzed amidation of aryl halides.

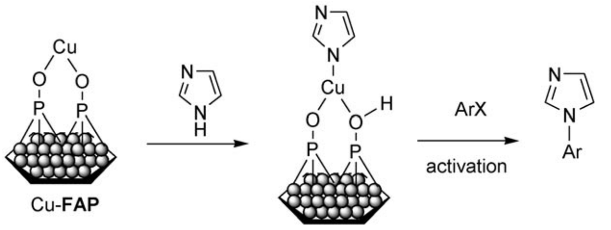
resulting radical anion $ArX^{\bullet-}$. Finally, on the basis of their data, which are not consistent with pathways B and C, these authors propose the remaining path A as the most reasonable. An aryl–copper(III) intermediate calculated to be kinetically accessible under the reaction conditions could be formed by a concerted oxidative addition or by internal electron transfer. The carbon–halogen bond would be cleaved within the coordination sphere of the copper center to afford the ArNu product.

Copper-catalyzed amidation was also studied in 2008 by Huffman and Stahl.[112] They prepared a previously described copper(III) complex, which features a Cu−C(aryl) bond within a macrocyclic chelate (Scheme 28) and showed that the latter was able to react with various amide nucleophiles to provide the corresponding N−C$_{aryl}$ coupling product. The reaction of the nucleophiles proceeds more rapidly with an electron-withdrawing p-NO$_2$ group on the ring (which corresponds to a more electrophilic Cu^{III} intermediate) than with an electron-donating substituent (p-Me). Additionally, reactions involving more-acidic N−H bonds are also more rapid, which might correspond to the fact that the deprotonation takes place during or before the rate-limiting step. These important results are in agreement with the often-speculated involvement of Cu^{III} species in the copper-catalyzed arylation of nucleophiles.



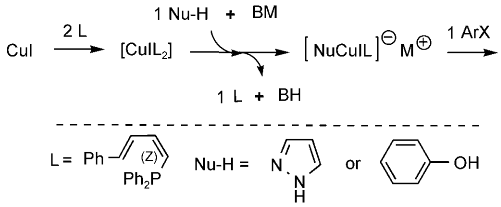
Scheme 28. An example of a precatalyst involved in the copper-catalyzed arylation of nucleophiles.

Most of the studies mentioned above are in agreement with coordination of the nucleophile prior to the activation step (by oxidative addition or electron transfer) of the aryl halide. This basic mechanism was also proposed by Choudary et al. in 2005 [Scheme 18, Eq. (51)]. The XPS and FTIR spectra were consistent with the preliminary coordination of the imidazole to a copper fluoroapatite before the aryl halide activation step (Scheme 29).[98]



Scheme 29. Coordination of imidazole to a copper fluoroapatite before ArX activation occurs.

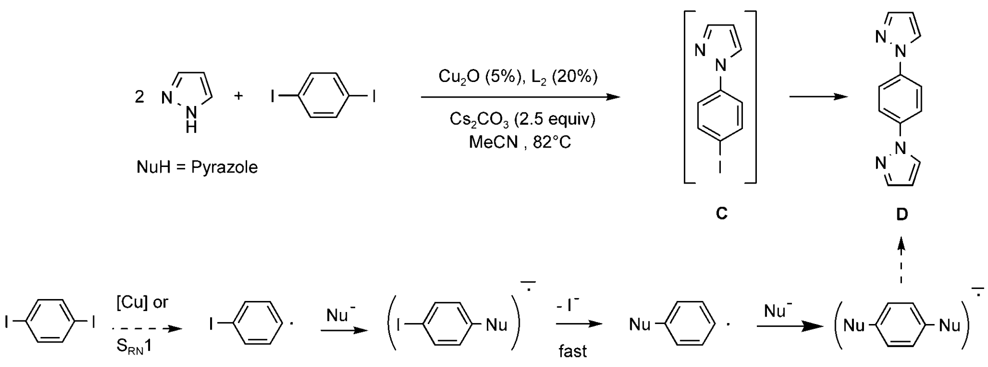
Buchwald and co-workers also suggested prior coordination of imidazole in a similar coupling performed in the presence of a phenanthroline-type ligand [Scheme 3, Eq. (5)].[23b] Our research group, on the basis of ^{31}P NMR data, recently described a possible pathway involving precoordination of the nucleophile (pyrazole or phenol) to the copper center as the first step in the coupling reaction (Scheme 30).[113]



Scheme 30. Coordination of imidazole or phenol to copper before ArX activation in the presence of butadienylphosphines.

After in situ formation of a [CuIL$_2$] complex, in which L represents a butadienylphosphine, the addition of one equivalent of pyrazole (NuH) and of two equivalents of base (BM = Cs$_2$CO$_3$) leads to the release of one equivalent of phosphine L. A precipitate is formed, to which the addition of PhBr (1 equiv) leads quantitatively to phenylpyrazole, thus confirming the presence of one pyrazole moiety coordinated to the copper center. It is noteworthy that if PhBr is first added to the [CuIL$_2$], the ^{31}P NMR spectra (solution and precipitate) remain unchanged.

As mentioned above, two conceivable mechanisms for the activation of ArX involve electron transfer (with radical intermediates) and oxidative addition. In 2004, we described results which excluded the participation of radical anion intermediates.[17] The tests performed included the classical diagnostic technique of monitoring the behavior of a dihalobenzene and its substitution products during a nucleophilic substitution reaction.[114] We observed that the coupling of

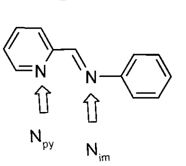


Scheme 31. Test for the intermediacy of radical anion intermediates in Ullmann-type condensations.

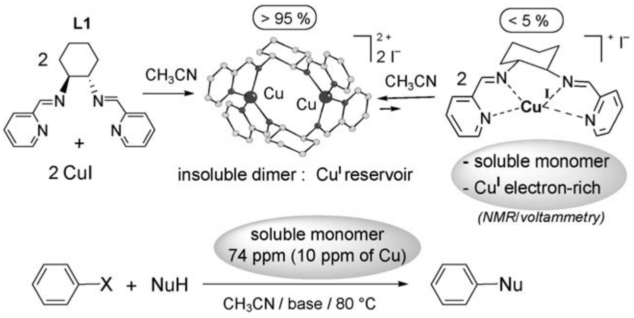
1,4-diiodobenzene to excess pyrazole initially gave rise to monosubstituted product **C** (Scheme 31), which underwent subsequent substitution to afford **D**. According to the reported mechanisms, a radical anion would have formed **D** without significant intermediacy of **C**, even with short reaction times.[115]

In another study we synthesized several bidentate ligands such as, for example, **L1** or **L14** (Schemes 1 and 8), with pyridine and/or imine nitrogen binding sites, and tested them in the arylation of phenols.[41c] This study highlighted the relationships between the structures of the chelates and their catalytic efficiency, and defined the role of each type of nitrogen binding site. For example, in the efficient ligand **L14**, the pyridine site intervenes in a step involving an electron-rich copper center (oxidative addition), while the imine is instead involved in steps for which a more electrophilic copper center is needed (nucleophilic substitution or reductive elimination). The synergy of both sites and a good balance between the electron-releasing and electron-withdrawing properties within the same ligand could explain its high efficiency. Further development of this approach could allow for a more rational design of efficient ligands in place of the classical ligand-screening approach.

L14



The interactions between ligands and copper are not well-understood in the copper-catalyzed arylations of nucleophiles. In a recent study we synthesized a precatalyst involving one of the most efficient ligands from the literature (**L1**), and characterized it in the solid state and in solution (X-ray crystallography, NMR, electrochemistry).[41d] We were thus able to describe the various stages taking place in the early phases of copper-catalyzed arylations of nucleophiles. The association of **L1** with copper(I) salts in acetonitrile lead to the formation of an insoluble dimeric complex that behaves like a copper(I) reservoir (Scheme 32). A very small fraction (less than 5 %) of the latter is soluble as the monomeric form. This monomeric species, in which the copper is in the (+I) oxidation state and made electron-rich by the ligand (NMR- and voltammetric studies), is the only soluble copper species present in solution at the beginning of the catalytic cycle. (less than 5 % of the copper introduced in the reaction mixture forms a soluble complex). On the basis of this study, at 80 °C, the arylation of 3,5-dimethylphenol (NuH) by iodobenzene (X = I) takes place whereas the only soluble copper species (the monomer) is present at very low concentration at the beginning of the reaction (ca. 74 ppm of monomer or 10 ppm of Cu, corresponding to a TON of ca. 3×10^5) (Scheme 32).[41b,d]



Scheme 32. Copper species involved in the copper-catalyzed arylation of nucleophiles. The monomer is the only soluble Cu species at the beginning of the arylation reaction.

A similar use of very low copper loading was obtained for the arylation of pyrazole (NuH) from PhI (X = I), still performed at 80 °C in presence of 0.035–0.05 mol % of Cu_2O and of 0.2–1 mol % of ligand **L1** or **L2** (Schemes 1 and 3).[17] In the case of pyrazole, when low catalyst loadings were employed, a higher ligand/catalyst ratio was of great benefit to obtain good yields. This high ratio was thought to statistically favor formation of the active catalyst species and to disfavor competitive complexation of compounds other than the coordination of ligands to copper.[17a] It is worth noting that apparently in the above described conditions, neither inhibition nor deactivation of the systems occurred in the course of the reaction.[41b,d]

5. Conclusion

It must be emphasized that, particularly in the case when electrophiles are activated aryl chlorides (but also with activated aryl bromides or iodides), the essential control experiments are often missing from the publications. This is a crucial point because in some cases, particularly for aryl chlorides, the experimental conditions are ideal for an S_NAr-type coupling mechanism. This means that in these cases the presence of copper may not be necessary at all. Greater vigilance and caution should be applied in the future in regard to this important point.

Major achievements have already been made since the renaissance of copper-catalyzed Ullmann reactions in the early years of this decade. However, significant challenges remain to be overcome to ensure ongoing development of this method (Figure 2), some of which are listed below:[6]

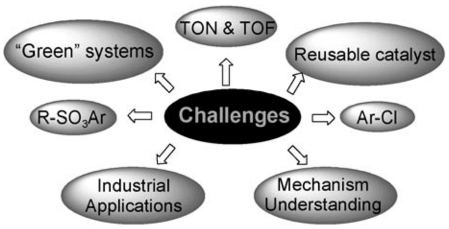


Figure 2. Stimulating challenges for Ullmann-type reactions. TON = turnover number, TOF = turnover frequency.

1. Discover new ligands or entirely new catalytic systems that work at lower catalyst loading ($\leq 1\,\%$ [Cu] mol) both in mild temperature conditions and with increased turnovers and turnover frequencies (shorter reaction times than those known). The goal here is to reduce the amount of wasted copper and to obtain more economically competitive systems. This goal could also be attained through the development of novel and efficient supported copper/ligand systems that are recoverable and reusable. Moreover, by trapping the metal, this concept would more easily result in low residual toxicity levels after work-up of the reaction mixtures. This last point is an important consideration for drug synthesis.
2. Find simple and original catalyst systems for use under environmentally friendly conditions. For example, "green" solvents as well as ligand-free or solvent-free reactions.
3. Discover efficient systems which allow for the replacement of aryl iodides and bromides by less reactive aryl chlorides or sulfonates. The chlorides are significantly less expensive, and the sulfonates could allow phenols to be generated in the Ullmann-type coupling reactions.

An important question concerns the industrial application of the modern catalytic version of the Ullmann reaction. It is difficult to get information from private industry, but we believe that this technology is going to find an important place. For example, the Sashun Chemical company produced the first few tonnes of a coupling product (C–N cross-coupling from aryl bromides) with one of our catalytic systems in 2007.

From general considerations, the lower cost of copper and the use of readily obtainable ligands provide indisputable advantages over the expensive palladium/ligand systems (often costly ligands are also used).[6] However, the two types of catalysis are complementary. Indeed, in terms of the challenges indicated above, it is noteworthy that palladium-catalyzed reactions have already been used successfully to give highly efficient systems. Moreover, mechanisms involving palladium catalysis are better understood than those of copper catalysis, for which comparatively few studies have been undertaken. Elucidating this mechanism could enable us to, at least partially, reach the objectives listed above. In the future, this point will probably constitute the most exciting challenge for the development of catalytic Ullmann reactions.

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