Conference paper

Xavi Ribas* and Imma Güell

Cu(I)/Cu(III) catalytic cycle involved in Ullmann-type cross-coupling reactions[1]

Abstract: Copper-catalyzed cross-coupling reactions for C–heteroatom bond formation have attracted numerous research groups in the past 15 years aiming at finding more efficient methodologies under milder conditions. The use of auxiliary ligands has tremendously improved Ullmann-type couplings although a general methodology for different heteroatom-nucleophiles is still lacking. Mechanistic insights are seen as a clue for designing new effective, broad-scope and general methodologies. In this review we describe the widely discussed mechanistic options for this reaction and the use of model compounds to unravel key mechanistic aspects for copper-catalyzed C–heteroatom transformations. Stable aryl-Cu(III) species in model systems are shown to be reliable active catalysts in the coupling of a broad nucleophile scope such as phenols, amides, sulfides, selenides, phosphites, halides and also activated methylene susbtrates for carbon–carbon couplings.

Keywords: catalysis; C–heteroatom bond formation; copper; cross-coupling reactions; mechanism; OMCOS-17.

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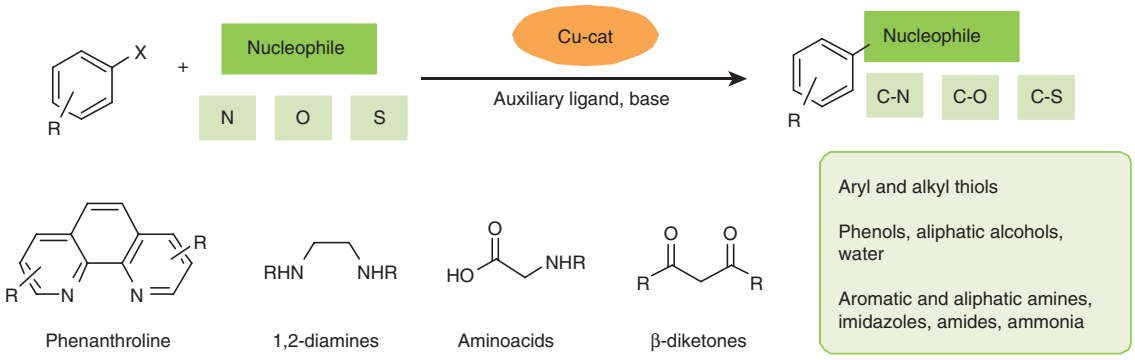
Introduction to Ullmann-type couplings

Modern Ullmann condensation reactions have re-emerged as reliable and efficient methods for the construction of C_{sp2}–heteroatom bonds [1–7]. There has been a gap of almost 100 years after Ullmann and Goldberg discovered the copper mediated arylation of amines or amides to construct new C-N bonds [8–10]. That was due to the requirement of stoichiometric amounts of copper, highly polar solvents, high temperatures (>200 °C) and long reaction times. The challenge of turning the reactions into the catalytic regime was faced by several groups at the beginning of the 21st century by using auxiliary ligands [11–18]. This was motivated in part by the need to go beyond palladium catalysis and use cheaper and environmentally friendlier first-row transition metals. Also, Pd-catalyzed Buchwald-Hartwig methodology was limited to arylation of amines [19, 20] despite lately the use of alcohols was also described [21, 22]. There exists a large number of ligands that have been used, although clearly binucleating N,N-, N,O- and O,O-ligands are the most utilized (for instance, phenanthrolines, 1,2-diamines, 1,3-diketones, iminopyridines and α-aminoacids, see Scheme 1) [4, 23]. Historically, Ullmann reactions commonly used Cu salts in stoichiometric amounts and no control was exerted over the coordination environment of the metal. By contrast, the presence of auxiliary ligands imposes a coordinative environment for the metal center, thus improving the stability of the active catalyst. Nonetheless, it is still unclear the exact nature of the catalytic active species in most of the systems; moreover, the coordinative properties of the heteroatom nucleophile have also a big impact in the in situ generation of the active catalyst. The most efficient catalytic transformations use low catalyst loadings (< 1 mol% Cu) and temperature may vary from room temperature to T > 130 °C. In general, most of the reactions occur under high concentration conditions and require a base, which is usually insoluble. The latter requirements convert the desired



Scheme 1 General Ullmann-type catalytic reactions.

mechanistic studies as truly challenging. In any case, the broad substrate and heteroatom nucleophile-scope have allowed for a wide implementation of Ullmann-type couplings in both academy and in industry [4, 23].

With all these precedents in hand, there is an enormous interest in unraveling the intrinsic mechanism for Ullmann couplings, aiming at having a detailed sequence of events and gaining understanding on the nature of key intermediates to refine the design of new auxiliary ligands. In the following sections the main mechanistic proposals will be covered and our contribution to the detection of aryl-Cu(III) species as active catalysts in model systems will be disclosed.

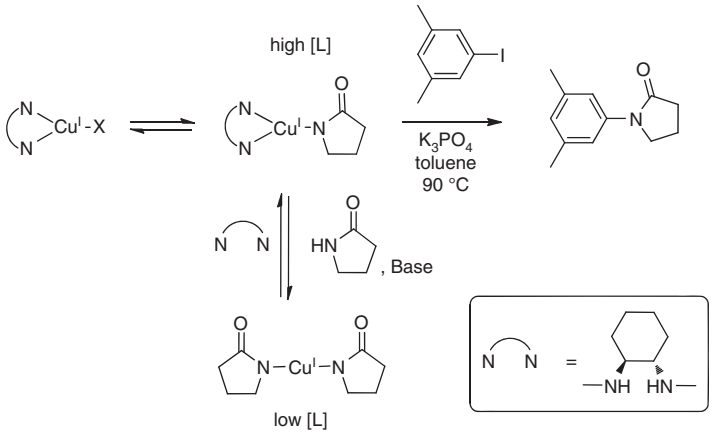
Structural characterization of the active catalyst

It is generally accepted that Cu(I) species are the active catalysts in Ullmann-type couplings. Therefore, despite examples using either Cu(0) or Cu(II) species as copper source are found, the in situ reduction or oxidation reactions occur to generate the active Cu(I) catalytic species. Furthermore, in most of the published mechanistic studies the presence of a base causes the deprotonation of the heteroatom nucleophile (H-Nuc) to readily form Cu(I)-Nuc species, which are usually proposed as the real catalyst of the reaction [7, 24, 25]. Some of the spectroscopically characterized Cu(I)-Nuc species are described below.

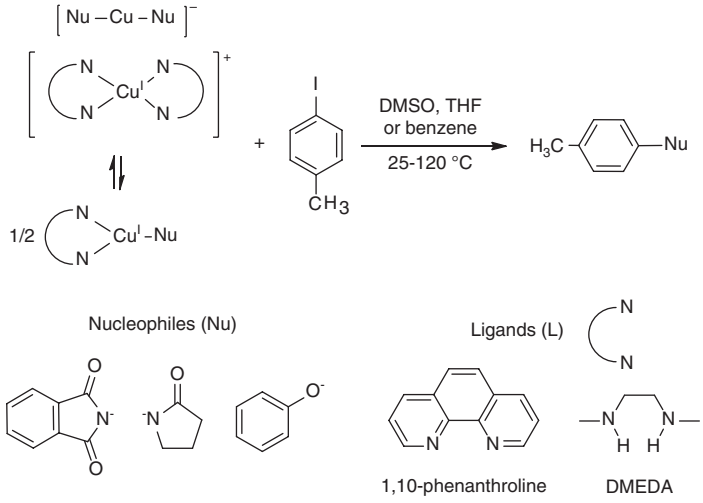
Buchwald studied in detail the copper-catalyzed amidation of 3,5-dimethyliodobenzene promoted by N,N-cyclohexyldiamine ligand [11, 26]. Mechanistic studies indicated that high ligand concentrations favor the formation of a copper(I)-amidate complex, which is a chemically and kinetically competent intermediate in the N-arylation reaction of the iodobenzene. On the contrary, low ligand concentrations favor the formation of copper species coordinatively saturated of amide ligands, thus rendering inactive species in the catalysis (Scheme 2). Guo and coworkers supported computationally these results by studying the coupling reaction between bromobenzene and acetamide using the catalytic copper(I)/ethylenediamine system [27]. They calculated the concentration of multiple ligated species in solution and predicted that the copper(I)-amidate complex was the major specie in the reaction mixture.

Hartwig and coworkers reported the synthesis and characterization of several copper(I)-imidate and copper(I)-amidate complexes as well as copper(I)-phenoxide complexes based on bidentate auxiliary ligands such as 1,10-phenanthroline, bipyridine, diamines and diphosphines [14, 15, 28]. NMR spectroscopy and conductivity studies revealed that complexes in solution exist as dimeric ionic species $[L_2Cu(I)][Cu(I)(nucleophile)_2]$ in equilibrium with neutral [LCu(I)(nucleophile)] species (Scheme 3). The three-coordinated neutral species were proposed to be the active intermediates for the formation of the corresponding N- or O-arylation coupling products. The anionic complex $[Cu(I)(nucleophile)_2]^-$ was described as unable to activate the haloarene since the independently synthesized complex $[Cu(I)(phth)_2][Bu_4N]$ was found to be inactive in the amidation reaction.

With all mechanistic studies in hand, the proposal involving the coordination of the nucleophile at the Cu(I) centre before the activation of the aryl halide is the most accepted one. The addition of auxiliary ligands



Scheme 2 Active Cu(I) species in the N-arylation of 2-pyrrolidinone using 3,5-dimethyliodobenzene.



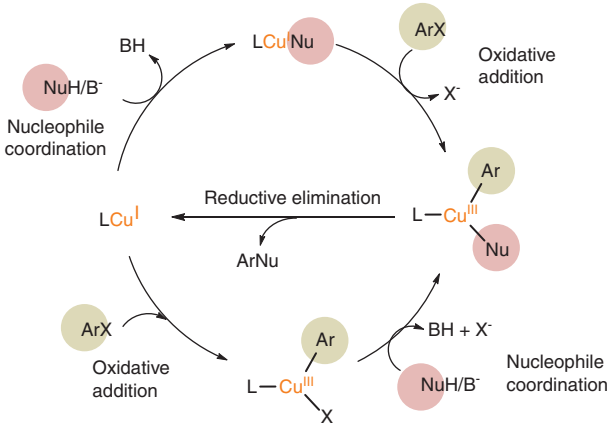
Scheme 3 Cu(I) species in equilibrium in the stoichiometric reaction of Cu(I)-imidate, -amidate and -phenoxide complexes with aryl iodides.

to copper salts in catalytic reactions prevents the formation of less reactive, multiply ligated cuprate structures [11, 26, 27, 29]. The synthesis of well-defined, stable and soluble copper(I) complexes has also been used as a proof of their utility as efficient catalysts in copper-catalyzed C–heteroatom bond formation reactions [30, 31]. Therefore, the nature and concentration of the auxiliary ligand used in Ullmann-type condensation reactions have a big impact in the equilibrium between different Cu(I) complexes present in solution as well as in the formation of the active catalysts.

The mechanistic pathway that these Cu(I)-Nuc active catalysts undergo upon reaction with aryl halide substrates is under discussion. The most relevant mechanistic proposals are described in the following section.

Activation of the aryl halide as limiting step

The activation of the aryl halide is usually thought as the rate limiting step in Ullmann-type couplings, thus the experimental detection of intermediates beyond this step is extremely challenging. Mechanistic propos-



Scheme 4 Cu(I)/Cu(III) catalytic cycle proposed for most Ullmann-type couplings. The initial formation of LCu(I)(Nu) species (upper cycle) is usually preferred although the initial aryl halide oxidative addition step cannot be discarded (lower cycle).

als have been basically published on the basis of kinetic data and computational studies [7, 25, 32]. The two main proposals involve a) a two-electron redox process involving a Cu(I)/Cu(III) catalytic cycle with aryl-Cu(III) as key species, or b) a one-electron redox process involving a Cu(I)/Cu(II) catalytic cycle with aryl radicals as key actors.

The main argument for proposing the Cu(I)/Cu(III) catalytic cycle in most Ullmann-couplings is the fact that catalysis are not affected by the introduction of radical traps. However, there are some exceptions to this general behavior, and examples of both are given below.

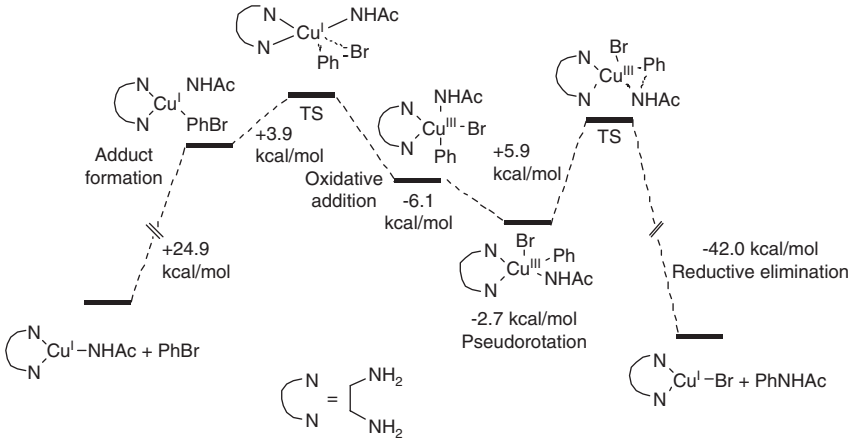
Two-electron Cu(I)/Cu(III) catalytic cycle

This mechanistic proposal involves a) the coordination of the nucleophile to the Cu(I) center, b) the aryl halide oxidative addition to form the aryl-Cu(III)-Nu species (with concomitant release of the halide anion), and c) the reductive elimination step to form the aryl-Nu coupling product and release the Cu(I) species ready to reenter the catalytic cycle (Scheme 4) [7, 25, 33]. The latter is the preferred proposal, although an initial oxidative addition step to form an aryl-Cu(III)-halide species followed by the halide exchange by the deprotonated nucleophile cannot be dismissed and is usually considered as a less probable mechanistic proposal (Scheme 4, lower cycle).

This Cu(I)/Cu(III) proposal is parallel to the classical Pd(0)/Pd(II) catalytic cycle proposed in Buchwald-Hartwig amination reactions [19, 20]. The presence of aryl-Cu(III) species as key intermediates was already proposed in the mid-70s by Cohen, based on the lack of inhibition upon addition of radical scavengers and on the retention of configuration in the homocoupling of vinyl halides [34, 35].

Based on simple DFT computational studies, Hartwig and coworkers have supported the intermediacy of aryl-Cu(III) complexes in several copper-catalyzed C–N and C–O bond forming reactions [14, 15, 28]. In a more detailed theoretical study based on a reaction previously reported by Buchwald experimentally, Guo calculated by DFT the oxidative addition/reductive elimination pathway in diamine ligated copper(I) amidate complexes with bromobenzene (Scheme 5) [27]. The aryl bromide oxidative addition at copper(I) afforded a pentacoordinated square-pyramidal aryl copper(III) intermediate. The latter contains the two coupling partners situated in *trans* position that switch to a cis-configuration by a pseudorotation step, finally allowing the reductive elimination step, which occurs with low energetic barrier. The oxidative addition was the rate limiting step of the Cu(I)-catalyzed aryl amidation.

The oxidative addition/reductive elimination pathway for the coupling of bromobenzene with methylamine catalyzed by copper(I)/acetylacetonate has been evaluated by Ding and coworkers [36]. They found that the active species is a neutral copper(I) complex containing both ligand and nucleophilic substrate and



Scheme 5 Guo DFT calculations for the oxidative addition/reductive elimination pathway in the arylation of acetamide using a diamine ligated Cu(I) catalyst.

the bromobenzene oxidative addition step was rate-limiting. Similarly, Jutand and coworkers proposed a Cu(I)/Cu(III) catalytic cycle for the amination reaction of iodobenzene with N-cyclohexylamine catalyzed by copper/2-acetylcyclohexanone system [37].

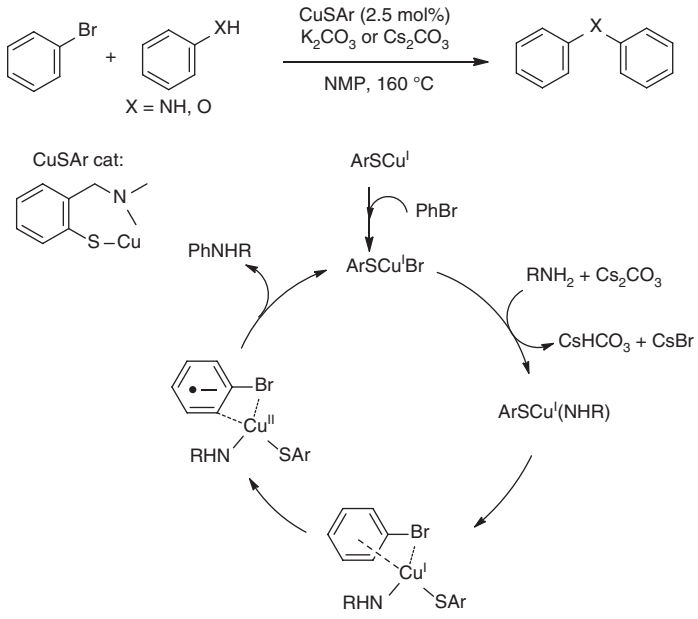
Strong support to the Cu(I)/Cu(III) proposal has recently come from model systems where catalytically active and well-defined aryl-Cu(III) species have been experimentally identified (see below).

One-electron Cu(I)/Cu(II) catalytic cycle involving aryl radicals

Although the mostly proposed mechanism for Ullmann-type catalysis is the Cu(I)/Cu(III) cycle, it has recently been proven by Peters and Fu groups that the alternative Single Electron Transfer (SET) activation of the aryl halide [38], which is a one-electron Cu(I)/Cu(II) cycle involving aryl radicals, is a viable mechanism in selected groups of C-Heteroatom coupling reactions performed under light irradiation.

Nevertheless, the SET proposal has been under discussion for many years because in a few cases the C-Heteroatom coupling catalysis was quenched by the use of radical traps. That was the case of van Koten's system, where aminoarenethiolato-Cu(I) complexes [Cu(I)SAr] were used as precatalysts in the cross coupling catalysis between bromobenzene and phenols or anilines (Scheme 6) [32, 39]. In those experiments, the use of radical traps stopped the reaction. Even in the late 70s, Hida and coworkers showed by EPR the formation of Cu(II) and bromoanthraquinone radical species in the Cu-mediated coupling of haloanthraquinones and 2-aminoethanol [40]. More recently, it was Buchwald and Houk that published a DFT study comparing all mechanistic possibilities for the copper-catalyzed N-arylation or O-arylation of 5-amino-1-pentanol with iodobenzene in the presence of a β-diketone or 1,10-phenanthroline as auxiliary ligands [41]. Their results suggested that the radical-involving SET mechanism was energetically favourable compared to an oxidative addition/reductive elimination Cu(I)/Cu(III) pathway. These results were however challenged by improved DFT calculations from the group of Fu using a different methodology [42].

But the proof for the existence of a SET mechanism in Ullmann-type couplings has come from Peters and Fu's labs by using photoirradiation. C-N coupling catalysis was achieved between carbazoles and aryl halides (iodo-, bromo- and chlorobenzene) by using a photoluminiscent copper(I)-carbazolide complex bearing two PPh_3 ligands as catalyst, which promotes the C-N coupling under light irradiation at room temperature [38]. The authors demonstrated that upon photoexcitation of the copper–carbazolide complex a copper-containing radical is formed, as detected by EPR spectroscopy. This radical intermediate reacts with aryl halides via SET to afford the corresponding C–N coupling product (Scheme 7). Strinkingly, radical clock test with o-(allyloxy)-iodobenzene afforded exclusive formation of cyclized compounds with no formation of the expected C-N



Scheme 6 van Kotens's system for C-N coupling catalysis with their proposal involving a SET mechanism.

coupling product (Scheme 7b). Furthermore, the same experiment using deuterated o-(allyloxy)iodobenzene afforded exclusive formation of cyclized compounds as a 1:1 mixture of diastereoisomers. The latter experimental evidences strongly support a SET mechanism for these Ullmann-type couplings (Scheme 7c).

Impressively, the same groups have expanded the substrate scope of these reactions to thiopenols for C-S couplings [43], to indole, benzimidazole and imidazoles for C-N couplings and to alkyl iodides for C-N couplings with carbazoles [44, 45]. In all these cases light irradiation is essential and reactions are performed between 0 to 25 °C.

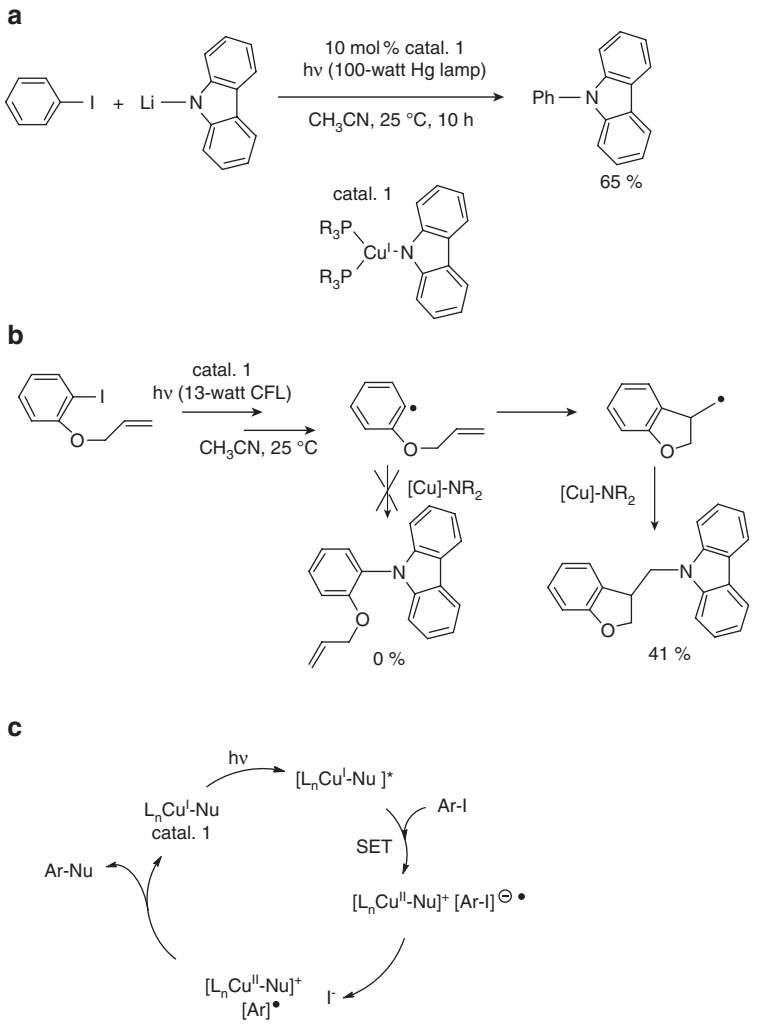
Other mechanistic proposals

There exist other mechanistic proposals for Ullmann-type coupling, although with far less experimental or theoretical support. In either σ-bond metathesis or π-complexation proposals the oxidation state of the metal remains as Cu(I) (Scheme 8). In σ-bond metathesis [46, 47], initially proposed by Bacon and Hill in the mid-60s, the Cu(I)-nucleophile species activates the aryl halide through a four-centered intermediate in which the Cu(I) center forms a σ-complex with the lone pair of electrons of the halogen atom. On the other hand, in the π-complexation proposal from Weingarten in the mid-60s as well [48, 49], the Cu(I) species interacts with the π-electrons of the aromatic aryl moiety instead of the those of the leaving halogen atom, and the formation of a Wheland arenium species facilitates the substitution of the halide by the nucleophile.

In any case, neither of these two additional proposals has been proven experimentally.

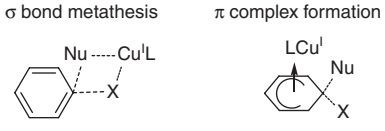
Trapping intermediates within model systems

The characterization of intermediate species in Ullmann-type catalysis has proven extremely challenging, as discussed in the previous sections. Our approach to gain mechanistic insight into these reactions is based on the use of model aryl halide substrates in order to direct the metal towards the activation of the aryl halide bond under mild conditions. To that end, we have been using triazamacrocyclic aryl halide substrates that place the Cu(I) center in very close proximity to the aryl-X bond [7, 50]. Under these conditions, we have dis-

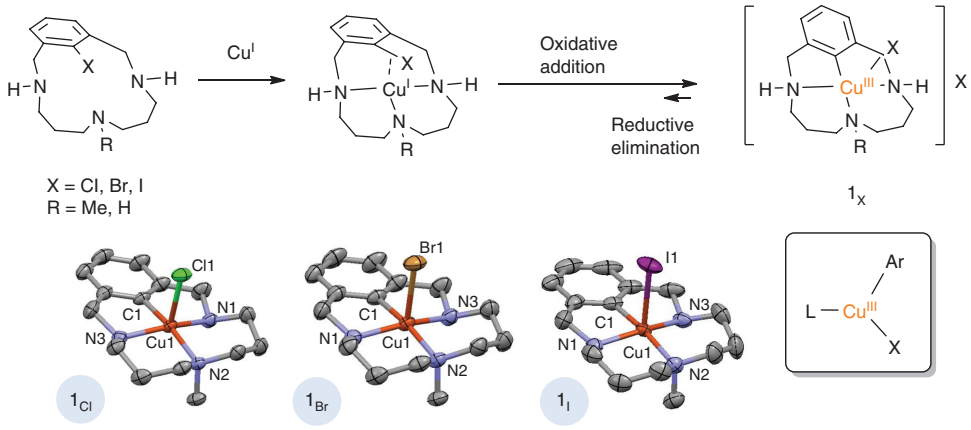


Scheme 7 Photoirradiated methodology for Ullmann-type C-N couplings described by Peters and Fu's groups. (a) Methodology, (b) radical clock experiment and (c) radical SET mechanism proposal.

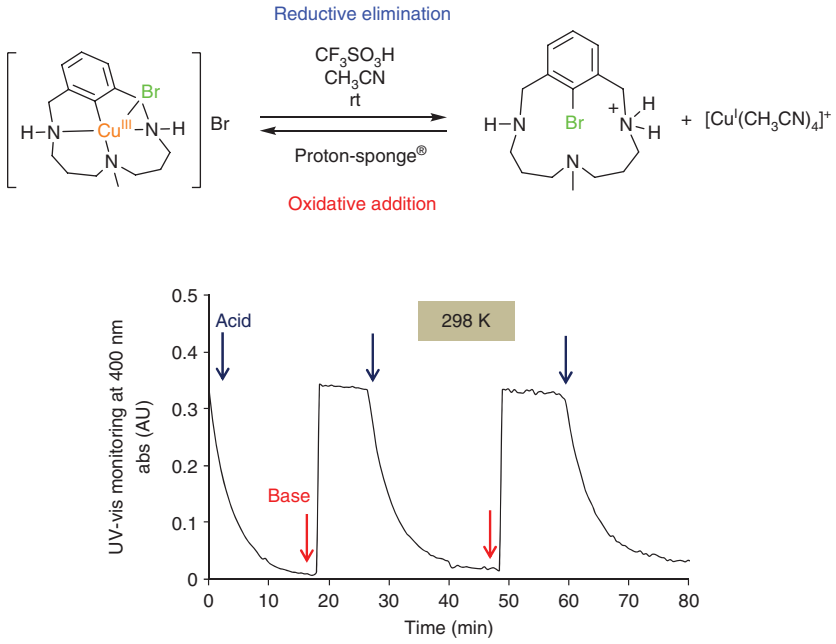
covered that the mechanism of activation of the substrate is the aryl halide oxidative addition, since we have been capable of isolating and fully characterizing the aryl-Cu(III)-halide species formed. Spectroscopic techniques (NMR, UV-vis, ESI-MS, Cu- K-edge XAS) have been used to fully understand these complexes, and even X-ray diffraction analysis has been performed (Scheme 9). The oxidative addition step is extremely facile and fast at room temperature within these systems, even for aryl-Cl model substrates. The corresponding aryl-Cu(III)-halide species are easy to crystallize and are stable at room temperature on the bench. Nevertheless, these compounds can also react under certain circumstances. A key reaction is the possibility to trigger the aryl-halide reductive elimination from these species by the addition of acid. The aryl-X and Cu(I) products can



Scheme 8 Mechanistic proposals for Ullmann-type couplings that do not involve any change in the oxidation state of the Cu(I) center.



Scheme 9 Triazamacrocyclic model aryl halide substrates that allowed the isolation and crystallization of the corresponding aryl-Cu(III)-halide species.

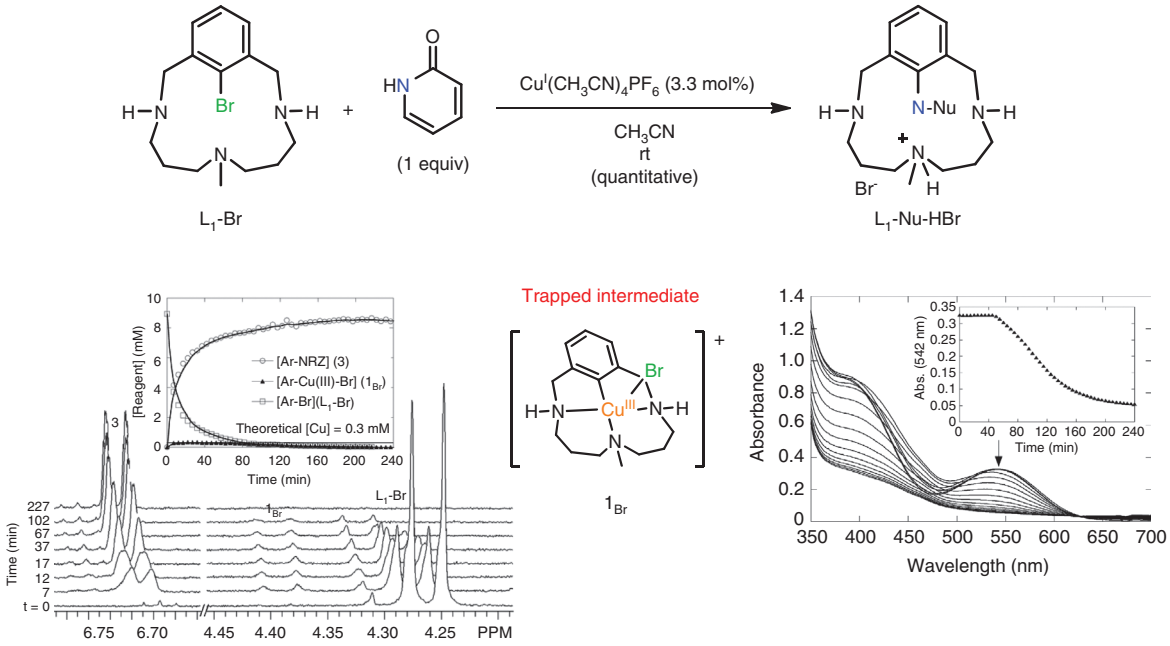


Scheme 10 Fundamental steps for two-electron Cu(I)/Cu(III) redox proposal. The graphic shows the UV-vis monitoring of the 400 nm band corresponding to the aryl-Cu(III)-Br species upon subsequent additions of acid and base, showing directly the key oxidative addition and reductive elimination steps.

reengage into the oxidative addition reaction by the action of a base, as monitored by UV-vis spectroscopy. Therefore, within this model systems it is possible to directly observe for the first time the two fundamental steps of two-electron Cu(I)/Cu(III) redox cycle proposed for Ullmann-type couplings (Scheme 10).

C–N coupling catalysis mediated by aryl-Cu(III) species

We were capable of demonstrating for the first time that a typical C-N coupling catalysis was taking place through the formation of aryl-Cu(III)-Br intermediate species [50]. For that purpose, we used a cyclic amide as N-nucleophile (pyridone) and a triazamacrocyclic aryl-Br as model substrate (Scheme 11). The catalysis was performed at room temperature using a 3.3 mol% of Cu(I) loading and in less than four hours the cataly-



Scheme 11 First Ullmann C-N coupling catalysis where the direct formation of a Aryl-Cu(III)-Br species has been in situ detected.

sis was finished and the C-N coupling product obtained quantitatively. Most importantly, the catalysis was spectroscopically monitoted by ^{1}H NMR and UV-vis, which revealed the formation of the aryl-Cu(III)-Br as the steady-state intermediate species during the catalysis. This result suggests that the rate-limiting step might be the exchange of the halide by the nucleophile at the apical position just before the reductive elimination takes place. Indeed, the C-N reductive elimination step had been previously proven to easily occur under stoichiometric conditions using isolated aryl-Cu(III) complexes and amide nucleophiles [51].

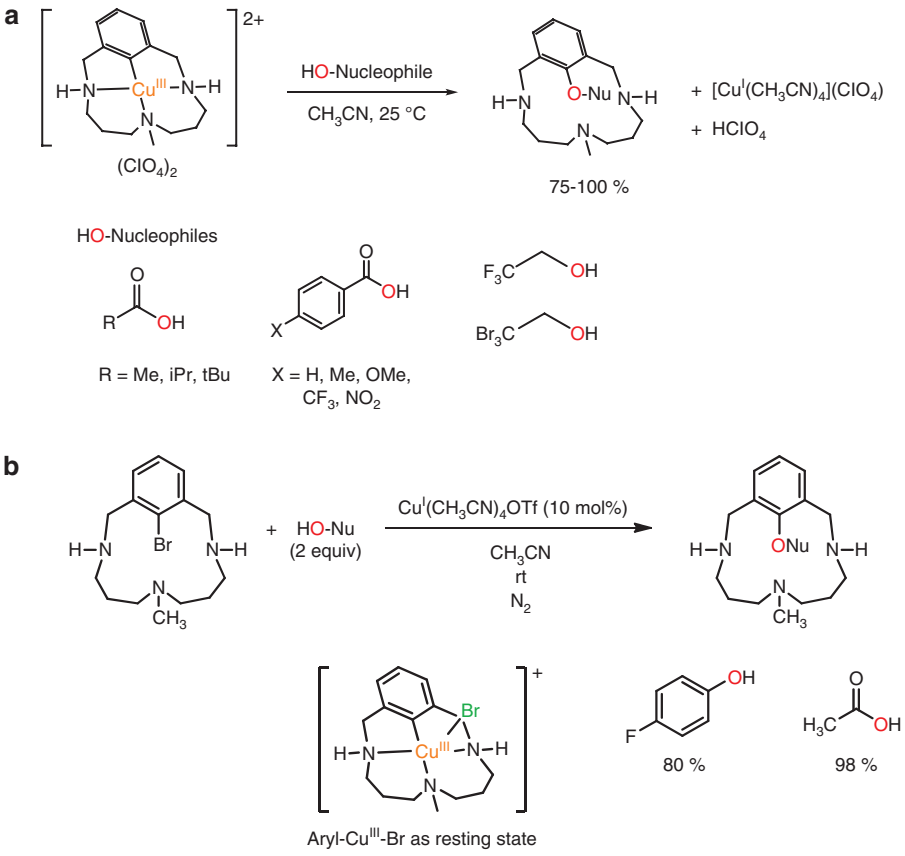
The model system described here allows for using low concentrations of the aryl halide substrate (around 10 mM), much less than the typical high concentrations for standard Ullmann couplings (>0.5 M). Furthermore, there is no need to use an external base to deprotonate the heteroatom nucleophile since the amine residues of the model substrate are thought to participate in the deprotonation step acting as basic centers.

With this important result in hand, we have expanded the scope of heteroatom nucleophiles to be engaged in coupling catalysis within our model system to prove the existence of a Cu(I)/Cu(III) mechanism for a variety of heteroatom nucleophiles, as described in the following sections.

C–O coupling catalysis mediated by aryl-Cu(III) species

The easy isolation of aryl-Cu(III) species [7, 52–55] allowed us to study their stoichiometric reactivity with HO-nucleophiles, i.e. phenols, aliphatic alcohols and carboxylic acids (Scheme 12) [56]. In all cases the reaction afforded the aryl-O coupling product quantitatively, thus validating the favourable reductive elimination step upon HO-Nu coordination to the aryl-Cu(III) species. However, the group of less acidic aliphatic alcohols tested, such as tert-butanol ($pK_{A\,(DMSO)}$ = 32.2), showed no reactivity with aryl-Cu(III) species, whereas trifluoroethanol ($pK_{A\,(DMSO)}$ = 23.5) afforded a 75 % yield in this stoichiometric reaction. That clearly suggested that the deprotonation of the HO-Nu was not possible and the reaction stopped.

Strikingly, we were capable of performing the C-O coupling under catalytic conditions using a 10 mol% of Cu(I) loading, the aryl-Br model substrate and p-fluorophenol and acetic acid as HO-nucleophiles. In both cases the catalytic reactions afforded good to excellent yields of coupling product and the aryl-Cu(III)-Br species was detected by UV-bis monitoring of the catalysis, thus proving its key role in the catalytic cycle.

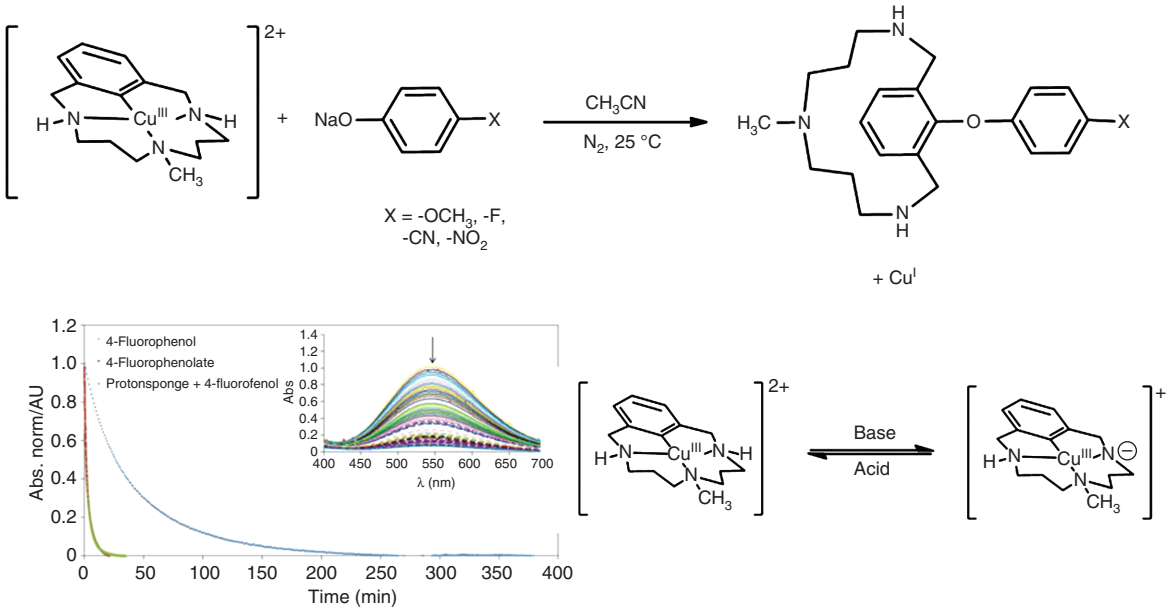


Scheme 12 (a) Study of the reductive elimination reaction between well-defined aryl-Cu(III) species and HO-nucleophiles. (b) First Ullmann C-O coupling catalysis where the direct formation of a Aryl-Cu(III)-Br species has been in situ detected.

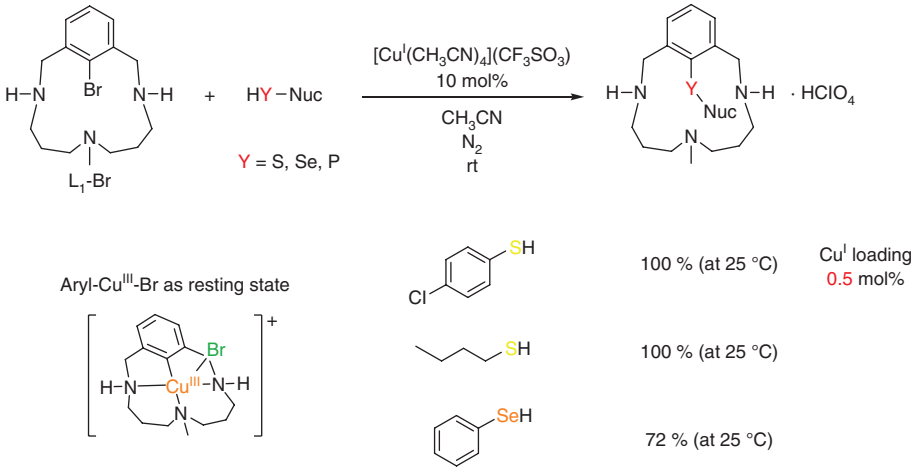
The presence of secondary amine moieties coordinating the Cu(III) center in our well-defined aryl-Cu(III) systems introduces the new concept of ligand reactivity, and specifically, the pH-dependent of the system due to its capability to act as a basic center upon decoordination or as an acidic center in front of stronger bases [57]. We have described that the reactivity of aryl-Cu(III) species in front of phenols or phenolates is completely different although the same coupling product is obtained. In the former, the deprotonation of the nucleophile linked to the protonation of a secondary amine is envisioned, whereas in the latter case the phenolate is capable to deprotonate the coordinated secondary amine (Scheme 13). Importantly, the reactivity with phenolate is one order of magnitude faster compared to phenol, thus, although under stoichiometric conditions, this might open another perspective concerning the pH-tunable reactivity of Cu(III) species. Mechanistic studies are needed to gain more insight into this particular reactivity.

C–S and C–Se coupling catalysis mediated by aryl-Cu(III) species

Thiophenols show an even faster reactivity with aryl-Cu(III) species than phenols. The catalytic version of the C–S coupling using our aryl-Br model system turned to be extremely facile at room temperature and very effective, with TON up to 200. *p*-Substituted thiophenols, aliphatic thiols and aromatic selenium derivatives (ArSeH) have been successfully used as S- or Se-nucleophiles to afford the corresponding coupling products at room temperature (Scheme 14) [58]. The resting state species in the conditions of the catalysis when model aryl-Br is used was the aryl-Cu(III)-Br, as ascertained by UV-vis.



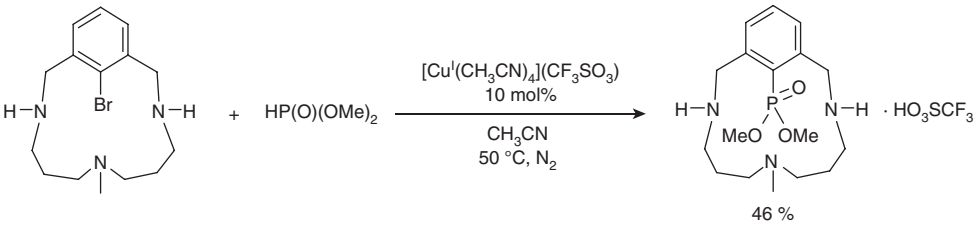
Scheme 13 Stoichiometric reactivity of aryl-Cu(III) species with phenolates. The plot shows the distinctively faster reaction of phenolates compared to phenols, as monitored by UV-vis following the 550 nm band of the deprotonated aryl-Cu(III) complex.



Scheme 14 Catalytic coupling of model aryl-Br with HS-Nuc and HSe-Nuc using down to 0.5 mol% of Cu(I) loadings. The in situ observation of the aryl-Cu(III)-Br species under catalytic conditions strongly suggests a two-electron Cu(I)/Cu(III) catalytic cycle.

C–P coupling catalysis mediated by aryl-Cu(III) species

For H-phosphonate diester bear an acidic HP-moiety that was envisioned as a good coupling partner in the reaction with well-defined aryl-Cu(III) species [58]. Indeed, different stoichiometric reactions were performed with $HP(O)(OR)_2$ (where R = Me, *n*Bu, $PhCH_2$) affording the desired coupling in quantitative yields for R = Me, $PhCH_2$, whereas for R = *n*Bu a top 48 % was obtained. These C-P bond forming reactions can be upgraded into a catalytic regime as is the case of H-phosphonate dimethyl ester, which afforded a 46 % yield upon heating to 50 °C and employing up to 2 equiv of substrate (Scheme 15). The slow addition of the substrate proved to increase the yield by minimizing the dimethyl phosphite decomposition. As expected, when these reactions were monitored by UV-vis spectroscopy, the product of the oxidative addition, aryl-Cu(III)-Br was observed as a steady-state intermediate.

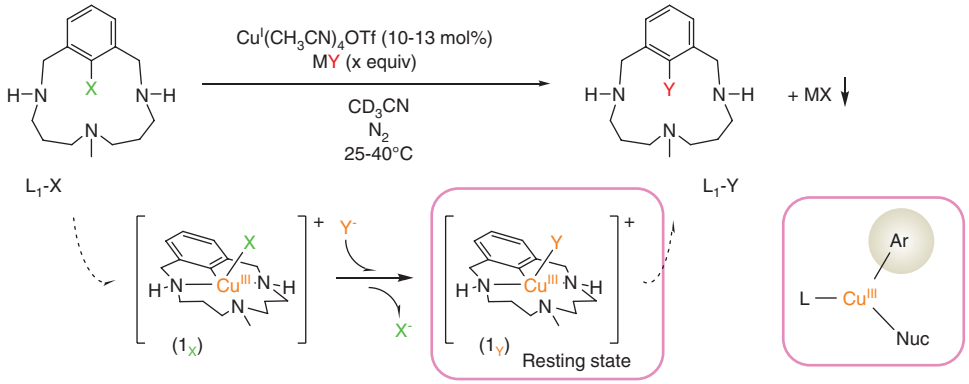


Scheme 15 Catalytic coupling of model aryl-Br with H-phosphonate diesters.

Halide exchange reactions (including fluorinations) catalyzed by aryl-Cu(III) species

The model system based on the aryl halide triazamacrocycle also allowed the detailed study of the halide exchange reactions. i.e. exchanging one halogen atom by another one [59]. This type of exchange has a big relevance on the ulterior reactivity of the aryl-X group, since the reactivity decreases in the order aryl-I > aryl-Br > aryl-Cl > aryl-F [60, 61]. Therefore, finding straightforward methodologies to achieve these desired transformations will be extremely useful in organic synthesis. Moreover, understanding the mechanistic details behind these transformations is indeed crucial to be able to design new methodologies. We have used our model system to a) achieve the desired catalytic halide exchange reactions among Cl, Br and I derivatives and b) unravel the mechanism of this catalysis.

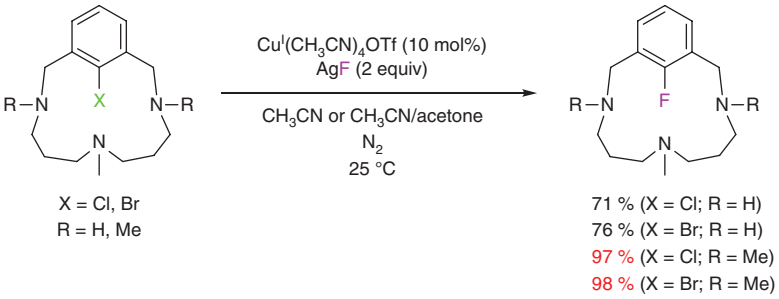
The selection of the halide salt to be used in excess in order to promote the aryl halide exchange is crucial (Scheme 16). We have observed that in the case of exchanging a heavier halide by a lighter one, tetrabutylammonium (TBA) halide salts (TBAY) are good reactants to obtain the desired exchanged aryl halide. On the contrary, in the case of exchanging a lighter halide by a heavier one, only NaY salts can perform the desired halide exchange. That indicates that the precipitation of NaX (where X is the exchange halide) is the major factor triggering the catalytic cycle when exchanging lighter halides by heavier one, whereas in the case of exchanging heavier by lighter, the higher strength of the aryl-Y bond is responsible for favoring the catalysis.



L_1-X	MY (equiv)	L_1-Y	% yield
L_1-I	Bu_4NCl (5)	L_1-**Cl**	96
	Bu_4NBr (10)	L_1-**Br**	87
L_1-**Br**	Bu_4NCl (10)	L_1-**Cl**	99

L_1-X	MY (equiv)	T (°C)	L_1-Y	% yield
L_1-**Br**	NaI (10)	25	L_1-**I**	84
L_1-**Cl**	NaI (10)	40	L_1-**I**	56
	NaI (10)	40	L_1-**I**	57
	NaBr (10)	25	L_1-**Br**	37

Scheme 16 Catalytic halide exchange reactions among Cl, Br and I halides. The aryl-Cu(III)-Y species has been detected in situ by UV-vis.



Scheme 17 Catalytic fluorination of model aryl-halide substrates involving the intermediacy of aryl-Cu(III)-X species.

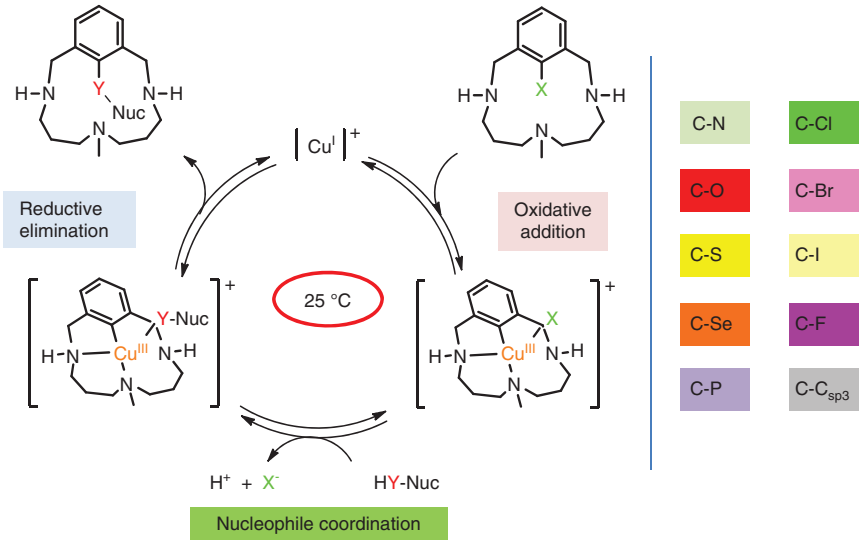
Nonetheless, mechanistically these reactions behave different than the C-N, CO, C-S, C-Se and C-P couplings mentioned in the previous sections [50, 56–58], because the resting state observed by UV-vis monitoring is not the product of the oxidative addition, but the subsequent exchange of the apical former halide by the new entering one. That indicates that the rate-limiting step has switched from the exchange of the halide by the entering nucleophile step to the final reductive elimination step.

Importantly, we also attempted the fluorination of our aryl-halide model substrates by using fluoride sources (AgF and KF) [59]. A slightly modified methodology was used, and slow addition of the AgF was performed to avoid deprotonation of the secondary amines due to the strong basicity of F^-. The aryl-F products were obtained in good yields (> 70 %), but those were increased to full formation of the fluorinated product when permethylated triazamacrocyclic aryl-halide model substrates were used (Scheme 17). The latter is in agreement with the detrimental side-reactions occurring due to the strong basicity of F^-. In this reaction the detected resting state was not the aryl-Cu(III)-F species but the aryl-Cu(III)-X, which was rationalized by means of DFT calculations that showed a low barrier for the aryl-F reductive elimination final step. Therefore, quantitative nucleophilic fluorination of aryl-X model substrates catalyzed by Cu(I) via aryl-F reductive elimination has been proven for the first time with a metal different than Pd, following a Cu(I)/Cu(III) catalytic cycle and under room temperature conditions. Given the relevance of nucleophilic fluorinations [62–65], this result might provide inspiration to develop Cu-based fluorinating methodologies with synthetic utility.

A common mechanistic picture for all C–heteroatom coupling catalysis within model aryl-X substrates

We have thus developed a family of copper-catalyzed C-Heteroatom bond forming reactions that can be rationalized under a common mechanistic picture (Scheme 18). This consists in a first aryl halide oxidative addition to form aryl-Cu(III)-halide species, followed by the exchange of the halide by the nucleophile at the apical position, and finally closing the cycle through a reductive elimination step from an aryl-Cu(III)-Nuc species [7].

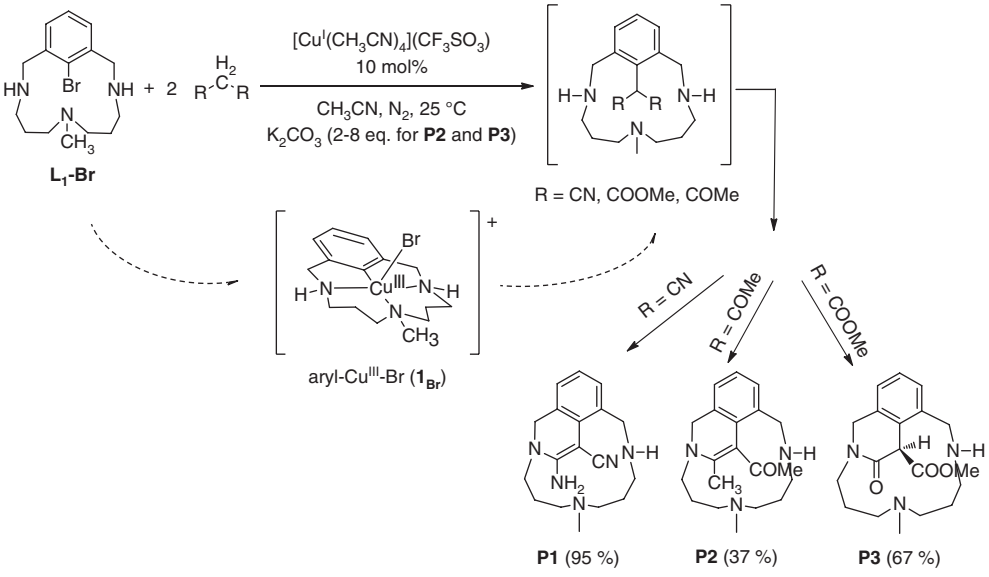
In this family of reactions, the model substrate undergoes a very facile oxidative addition, thus differing from standard Ullmann couplings, where the activation of the aryl halide is usually rate-limiting. In the described reactions, we have generally observed that the rate-determining step is related to the nucleophile coordination. This has allowed the in situ observation for the first time of the oxidative addition product, aryl-Cu(III)-X species, under catalytic conditions. Only in the case of halide exchange catalysis, the resting state observed was the corresponding aryl-Cu(III)-nucleophile species (see Scheme 4). Regarding the mechanism, this model system serves as a platform to demonstrate that the two-electron Cu(I)/Cu(III) catalytic cycle is viable and indeed can occur at room temperature conditions, thus avoiding the harsher conditions usually required in standard Ullmann catalysis. Wang and coworkers have described stable aryl-Cu(III) species using a azacalix[1]-arene[3]pyridine macrocyclic environment, where they demonstrate a variety of C-heteroatom bond formation reactions by stoichiometric reductive elimination processes [66–69].



Scheme 18 Common mechanistic picture for the C–heteroatom bond formation via a Cu(I)/Cu(III) catalytic cycle using model aryl halide substrates.

Expanding the Cu(I)/Cu(III) catalysis to C–C Hurtley coupling reactions

Finally, we have also explored the chemistry of our system in the copper-catalyzed α-arylation of activated-methylene compounds [70], which are C_{sp2}-C_{sp3} bond forming reactions known as Hurtley couplings [3, 71–74]. Initial stoichiometric reactivity of the well-defined aryl-Cu(III) species with malononitrile, acetylacetone and dimethylmalonate afforded the desired C_{sp2}-C_{sp3} products, although subsequent intramolecular cyclization took place to produce the final products, namely 1,2-dihydroisoquinoline (compounds P1 and P2) and 1,2-dihydroisoquinolin-3(4H)-one (compounds P3) heterocycles. The catalytic version of these reactions was achieved and the same final products were obtained in moderate to excellent yield (Scheme 19). The reactions occurred by intermediacy of the aryl-Cu(III)-Br species, as detected by UV-vis monitoring of the catalysis. This demonstrates that the Cu(I)/Cu(III) redox pair is also competent for C–C coupling catalysis (Scheme 18).



Scheme 19 C_{sp2}–C_{sp3} Hurtley catalysis using model aryl halide substrates. Aryl-Cu(III)-Br is detected as resting state of the catalysis and intramolecular cyclization occurred to afford the final heterocyclic products.

Conclusions

Understanding the mechanistic details of Ullmann-type couplings remain a challenge for standard Ullmann catalysis. Among all mechanistic proposals, the two-electron redox pathway, namely a Cu(I)/Cu(III) catalytic cycle, is generally proposed. Indeed, we have been able to prove that the Cu(I)/Cu(III) cycle is feasible even at room temperature when model aryl halide substrates are used. On the other hand, the one-electron redox pathway involving aryl radical species has recently been proved for different nucleophiles under light irradiation conditions. Thus it is clear that more efforts are needed to unravel the mechanism of standard Ullmann-couplings with the final goal of finding a general and broad scope procedure to convert Ullmann catalysis as the best sustainable method of choice for C–heteroatom coupling reactions.

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