The mechanism of the modified Ullmann reaction†

Elena Sperotto,[a] Gerard P. M. van Klink,[a] Gerard van Koten*[a] and Johannes G. de Vries*[b]

Received 17th June 2010, Accepted 18th August 2010
DOI: 10.1039/c0dt00674b

The copper-mediated aromatic nucleophilic substitution reactions developed by Fritz Ullmann and Irma Goldberg required stoichiometric amounts of copper and very high reaction temperatures. Recently, it was found that addition of relatively cheap ligands (diamines, aminoalcohols, diketones, diols) made these reactions truly catalytic, with catalyst amounts as low as 1 mol% or even lower. Since these catalysts are homogeneous, it has opened up the possibility to investigate the mechanism of these modified Ullmann reactions. Most authors agree that Cu(I) is the true catalyst even though Cu(0) and Cu(II) catalysts have also shown to be active. It should be noted however that Cu(I) is capable of reversible disproportionation into Cu(0) and Cu(II). In the first step, the nucleophile displaces the halide in the LnCu(I)X complex forming LnCu(I)ZR (Z = O, NR′, S). Quite a number of mechanisms have been proposed for the actual reaction of this complex with the aryl halide: 1. Oxidative addition of ArX forming a Cu(III) intermediate followed by reductive elimination; 2. Sigma bond metathesis; in this mechanism copper remains in the Cu(II) oxidation state; 3. Single electron transfer (SET) in which a radical anion of the aryl halide is formed (Cu(I)/Cu(II)); 4. Iodine atom transfer (IAT) to give the aryl radical (Cu(I)/Cu(II)); 5. π-complexation of the aryl halide with the Cu(I) complex, which is thought to enable the nucleophilic substitution reaction. Initially, the radical type mechanisms 3 and 4 where discounted based on the fact that radical clock-type experiments with ortho-allyl aryl halides failed to give the cyclised products. However, a recent DFT study by Houk, Buchwald and co-workers shows that the modified Ullmann reaction between aryl iodide and amines or primary alcohols proceeds either *via* an SET or an IAT mechanism. Van Koten has shown that stalled aminations can be rejuvenated by the addition of Cu(0), which serves to reduce the formed Cu(II) to Cu(I); this also corroborates a Cu(I)/Cu(II) mechanism. Thus the use of radical clock type experiments in these metal catalysed reactions is not reliable. DFT calculations from Hartwig seem to confirm a Cu(I)/Cu(III) type mechanism for the amidation (Goldberg) reaction, although not all possible mechanisms were calculated.

[a]*Organic Chemistry & Catalysis, Utrecht University, Padualaan 8, 3584, CH, Utrecht, NL. E-mail: g.vankoten@uu.nl; Fax: +31 30 252 3615*
[b]*DSM Innovative Synthesis BV, A unit of DSM Pharma Chemicals, P.O. Box 18, 6160, MD, Geleen, NL. E-mail: Hans-JG.Vries-de@dsm.com; Fax: +31 46 4767604*

† Based on the presentation given at Dalton Discussion No. 12, 13–15th September 2010, Durham University, UK.

1. Introduction

1.1 The Ullmann reaction

In the early 1900's, Fritz Ullmann and Irma Goldberg reported their pioneering work on copper-mediated aromatic nucleophilic substitution reactions.[1–3] The original protocol for the coupling

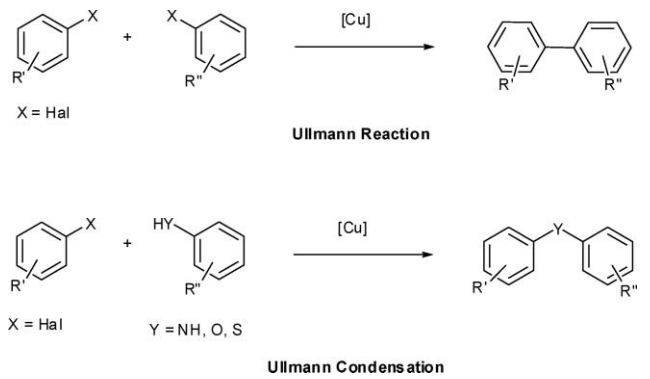
Elena Sperotto

Elena Sperotto was born in Sandrigo, Italy, and studied chemistry at the University of Padova where she received her Masters degree in 2003. Afterwards, she spent one year at DSM Research in Geleen, The Netherlands, for a post-graduate research project on enzymatic resolution of amino acids. She then worked on her PhD thesis at Utrecht University, The Netherlands, under the supervision of Prof. G. van Koten, where she investigated copper-catalyzed carbon-heteroatom coupling reactions, until receiving her doctorate in September 2009.

Gerard van Koten

Gerard van Koten is a Distinguished University Professor of Utrecht University. From 2005 to 2007 he was Dean of the Faculty of Science at Utrecht University. In 2007 he became Distinguished Research Professor (part-time) at Cardiff University (UK). His research comprises the study of fundamental processes in organometallic chemistry and the application of organometallic complexes as homogeneous catalysts. Recent interests are the immobilization of catalysts on dendrimers and on inorganic supports as well as the use of these materials for tandem catalysis. This also includes the development of novel enzyme–organometallic hybrid catalytic materials.

reaction required the use of stoichiometric amounts of copper salts together with high reaction temperatures (≥ 200 °C) and long reaction times. In spite of this, numerous industrial applications, such as synthesis of intermediates in pharmaceutical, agrochemical, fine and polymer chemistry were found over the years.[4–7] According to commonly accepted nomenclature, the term 'Ullmann condensation reaction' refers to a copper-mediated (stoichiometric or catalytic) reaction between an aryl halide and an amine, phenol or thiophenol to synthesize the corresponding aryl -amine, -ether or -thioether compounds, respectively. With the 'Ullmann reaction', though, the copper-mediated synthesis of biaryls from aryl halides is described (Scheme 1).[8–11]



Scheme 1 Schematic representation of the Ullmann reaction and the Ullmann condensation.

Two related reaction types exist known as the Goldberg and Hurtley reactions. The Goldberg condensation reaction involves the copper-mediated reaction between an aryl halide and an amide, to form a new C(aryl)–N bond,[12] whilst the copper-catalyzed condensation of 2-halobenzoic acids with various β-dicarbonyls (1,3 diketones) is called the Hurtley reaction.[13]

The recent interest in Ullmann chemistry has been spurred by the tremendous success of the palladium catalysed cross coupling reactions between haloarenes and nucleophiles, such as the Hartwig–Buchwald amination reaction, that were developed during the past 20 years.[14–18] An obvious concern for large scale applications of this type of chemistry is the cost of the metal and the ligands as well as the need for fully removing the metal from the product solution. The recent quest for cheap and sustainable reactions made many researchers turn their attention again to the copper-mediated cross-coupling reactions. The successful development of improved catalytic versions of this grand old chemistry has caused a veritable 'renaissance' of what is now known as the 'modified Ullmann reaction'. Many drawbacks of the classical reaction (*e.g.* the high reaction temperatures, long reaction times, high metal loadings, and narrow scope) have been overcome and a wide range of new procedures became available for applications in many areas.[19–26] The key of the 'modified Ullmann' procedure lies in the addition of ligands to the copper catalyst in order to improve the solubility of the copper precursors, leading to the use of milder reaction conditions, *i.e.* lower reaction temperature and time, lower catalyst loadings, and a widened scope of reactivity. In general the copper (pre-)catalyst is prepared by the *in situ* mixing of a copper salt and a suitable, often bidentate, chelator[19–26] such as diamines,[27–29] amino acids,[25,30,31] 1,10-phenantrolines,[32–37] diols[38–40] and other nitrogen- and oxygen-containing ligands.[41–44] These developments have been so successful that the modified Ullmann reaction has already found its way into large-scale production.[45] It is clear that this technology is much cheaper than the highly successful palladium-catalyzed variants. There is one major difference, however; whereas the palladium-catalysed Hartwig–Buchwald arylation is mechanistically well-understood there appears to be no consensus yet on the mechanism of the modified Ullmann reaction.

1.2 General aspects of copper chemistry

As a late transition element, copper occurs in a range of oxidation states (Cu(0), Cu(I), Cu(II), Cu(III) and Cu(IV)), and the ions readily form complexes yielding a variety of coordination compounds. Oxidation states I and II are known for many compounds and are the most common, while compounds with copper in oxidation state III are fewer in number.[46–48] Compounds containing Cu(0) species have been observed under particular conditions[49] and oxidation state IV exists only in a specific environment, in fluorides and oxides.[50,51]

Copper(I) is unstable in aqueous solution, according to the reported oxidation potentials ($Cu^+ + e^- \rightarrow Cu$ $E_0 = 0.52$ V; $Cu^{2+} + e^- \rightarrow Cu^+$ $E = 0.162$ V),[52] leading to a disproportionation equilibrium: $2Cu(I) \leftrightarrows Cu(0) + Cu(II)$. However, the relative stabilities of Cu(I) and Cu(II) in solution strongly depend on the nature of their anions and ligands and may vary considerably with solvents.

These considerations have a bearing on the difficulty of pinpointing an individual oxidation state involved in a specific reaction, since copper is likely to be present at more than one oxidation level, proportions of which may alter during the reaction as a result of redox processes. Moreover, many solvents and ligands show an outstanding coordinating effect with regard to copper, and thus they can influence the equilibria involved in solution. Copper ions not only undergo complex formation with molecules/anions present in the reaction system, but they often associate to form higher aggregated species.[54] In addition, both heterolytic and homolytic mechanisms have been suggested for

Hans de Vries

Hans de Vries received a PhD in Organic Chemistry from the University of Groningen with R. M. Kellogg. After a postdoc at Brandeis University in the US with Jim Hendrickson his first job was as a medicinal chemist with Sandoz in Vienna and London. Since 1988 he works for DSM in Geleen, The Netherlands where he is a Principal Scientist in Homogeneous Catalysis. In 1999 he was appointed part-time professor at the University of Groningen. He is also a visiting industrial professor at the University of Bristol. His research interests are homogeneous catalysis and catalysis for renewables.

reactions involving copper species, but telling between the two is complicated by the possible copper mediated electron transfer between organic intermediates of ionic and radical type (*i.e.* $R^{\bullet} + Cu^{2+} \rightarrow R^{+} + Cu^{+}$).[55] Therefore, the elucidation of the reaction mechanism for copper-mediated processes often appeared to be cumbersome and has led to conflicting mechanistic proposals, sometimes even for the same reaction.

In this perspective, we review the mechanistic studies reported for the Ullmann condensation reaction since its discovery and we present an overview of the possible and proposed mechanistic pathways for copper-catalyzed aromatic nucleophilic substitution reactions in homogeneous systems. Understanding the mechanism of this reaction could lead to important advances in this field and will probably allow further progress in the application of the modified Ullmann reactions.

2. Mechanistic investigations on the Ullmann condensation

Since the original work of Ullmann and Goldberg, it has been known that various copper sources are effective in the C–C and C–X coupling reactions, ranging from Cu(I) to Cu(II) salts, and even including metallic copper.[1–3] Comparisons among the various systems studied, mainly for C–N and C–O bond formations, led authors to conclude 'that almost any copper or copper compound may be used as a source of catalyst'[56] with similar behaviour, even though the use of Cu(I) salts appeared to lead to higher reactivities. The conclusion was that probably a single catalytically active species emanated from all these precursors. Therefore, the question of which oxidation state of copper is present in the active catalyst was the first to catch the interest of the scientific community. Studies on the formation of diphenyl ether from bromobenzene and potassium phenoxide using electron paramagnetic resonance (EPR) spectroscopy led to the hypothesis that the cuprous salt (Cu^{+}) was the true catalytic species and that the cupric salt (Cu^{2+}) was reduced to Cu^{+} by the phenoxide ions.[57] In 1987, Paine published a more systematic investigation on the catalytic species in the Ullmann synthesis of triarylamines.[58] In his work, he reported the results of experiments using homogeneous and heterogeneous catalysts having three different oxidation states of copper. When Cu(II) precursors were used, the catalytic activity was attributed to Cu(I) species, derived from the reduction of the cupric ions present, similarly to Weingarten's proposal.[57] The evidence for this hypothesis was the observed oxidation of the nucleophile diphenyl amine to tetraphenylhydrazine. Another example of ligand/nucleophile oxidation was reported by Aalten *et al.* as part of their investigation on the synthesis of anisole derivatives from the chloroarene using sodium methoxide.[59] Examining Cu(0) as precursor, Paine found, *via* scanning electron microscopy (SEM), that the surface of metallic copper is covered by a thin layer of Cu_2O. Upon coordination of the amine, which is not only the substrate but also a ligand, Cu_2O can leach into the solution and be active as Cu(I) precursor. More recently, Jutand and co-workers showed that 2 eq. of Cu(0)/1,10-phenanthroline can react with aryl halides to form Cu(I)phenanthroline and the aryl anion which is protonated to the arene.[60] These results and other considerations from Paine's work supported the role of Cu(I) in the Ullmann-type reaction, and at present Cu(I) ions are generally accepted as the primary catalytic species.[60]

The other steps in the catalytic cycle have generated more controversy. Since its discovery, the major debate involved with the Ullmann reaction always focused on the mechanism of the aryl halide activation step.[19–26,60–62] None of the reported proposals received a universal consensus from the scientific community, but only numerous and long standing questions. As will be seen in the next sections, diverse mechanistic suggestions have been reported and supported by experimental investigations, but evidence against each of them has also been described.

2.1 Proposed mechanistic pathways: historical overview

On the basis of a historical overview of the literature,[63] one can recognize four different classes of mechanisms proposed for the Ullmann condensation reaction. They will be discussed in the next sections. The different proposals can be classified into two main categories: those in which the oxidation state of copper changes throughout the mechanistic cycle and those in which the oxidation state remains constant. The four different alternatives involve:[64]

(1) Oxidative addition of ArX on copper(I) resulting in an intermediate Cu(III) species.

(2) Aryl radical intermediates, either *via* single electron transfer (SET) or *via* halide atom transfer (AT).

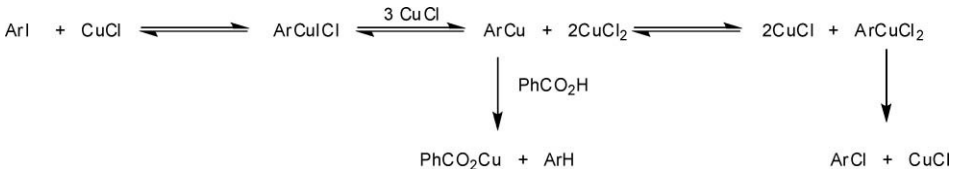
(3) σ-bond metathesis through a four-centre intermediate.

(4) π-complexation of copper(I) on ArX.

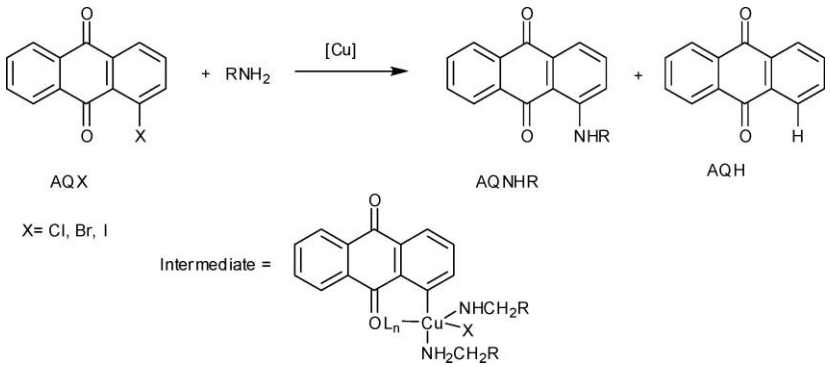
Clearly, alternatives (1) and (2) belong to the first category in which the copper species changes its oxidation state during the catalytic cycle, whereas (3) and (4) belong to the second category in which the copper species maintains the same oxidation state through the whole cycle.

2.1.1. Mechanistic pathways involving oxidative addition/reductive elimination. Several literature reports evoke the involvement of copper(III) intermediates in the Ullmann reaction mechanism. Although the existence of copper(III) complexes has been questioned for a long time, nowadays multiple examples are known.[48,51,65,66] The first to propose this type of organocopper(III) intermediates was Cohen, supported by previous studies performed on organocuprates.[67–69] In his first report,[70] he investigated the reaction of *o*-iodo-*N*,*N*-dimethylbenzamide with CuCl in DMF. Upon addition of benzoic acid, the reaction products found were *N*,*N*-dimethylbenzamide and the substituted product *o*-chloro-*N*,*N*-dimethylbenzamide. He observed that with an increase of benzoic acid concentration, formation of *N*,*N*-dimethylbenzamide increased, while the Cl-substituted product decreased. Similarly, after addition of $CuCl_2$, he noticed an increase of *o*-chloro-*N*,*N*-dimethylbenzamide production and a decrease of *N*,*N*-dimethylbenzamide. To explain the observed behaviour of the reaction, he proposed a pathway *via* the oxidative addition of the carbon-halogen bond to the cuprous chloride, leading to copper(III) organometallic intermediates (see Scheme 2).

With this proposal, he ruled out the possibility of a four-centred intermediate (aryl-halide-nucleophile–Cu) as this mechanism would not account for the observed reactivities. Moreover, radical intermediates were also excluded, because of the absence of *N*-methylbenzamide, which should have derived from the *ortho*-aryl radical *via* rapid hydrogen abstraction from the methyl group. Van Koten *et al.* reasoned against Cohen's conclusions, because 'this mechanism did not take into account the known chemistry of arylcopper(I) compounds'.[6,71,72] In particular, the absence of ArH



Scheme 2 Cohen's mechanistic proposal involving organocopper(III) intermediates.



Scheme 3 Bethell's proposal for the Cu(III)-intermediate in the reaction of halogenoanthraquinone with primary amines.

and coupled products Ar–Ar, expected to be formed during the reaction especially under the particular conditions used, seemed to make a mechanism invoking the formation of organocopper intermediates less likely. Instead he proposed these reactions to take place at the "surface" of mixed valence copper halide species.

Following Cohen's work,[73,74] other authors invoked the presence of arylcopper(III) intermediates in their proposed pathways.[75–77,61] In particular, Bethell investigated the reaction of some primary amines (RNH_2) with 1-halogenoanthraquinones (AQX) promoted by copper salts in acetonitrile, and he detected two different products, the aminated anthraquinone (AQNHR) and the dehalogenated one (AQH).[75] He then observed some particular features: (i) the reaction rate was dependent on the nature of the leaving halogen X (I > Br > Cl), but it didn't affect the product ratio (AQNHR:AQH); (ii) *N*-deuteration of the amine gave a small kinetic isotopic effect and did not affect the product ratio, whereas deuteration on the α-carbon of the amine led to the observation of an isotope effect and a large increase in the formation of the aminated product (AQNHR). He explained these observations by the intermediacy of an arylcopper(III) complex bearing one or more amine ligands and one amide ligand (Scheme 3).

Bethell also noticed that the ratio of aminated to dehalogenated products was directly proportional to the concentration of the free amine present in the reaction. He then interpreted these results considering that the partitioning of products derived from the competition between an intermolecular amination and intramolecular hydrogen transfer from the C–H bonds of the amide ligand, which would account for the formation of AQH.

To summarize the various reports which invoked the same mechanism, a current representation for two potential oxidative addition/reductive elimination mechanistic pathways can be depicted as shown in Fig. 1.

In one proposal for this catalytic cycle, the first step is an oxidative addition of the aryl halide to copper, to form a copper(III) intermediate. Subsequently, the halide on copper is exchanged for the nucleophile and the obtained intermediate, *via* a reductive elimination step, releases the coupling product and the active Cu(I) catalyst is regenerated. Unlike palladium(0) catalyzed cross-couplings, in which the oxidative addition step is considered to precede the transmetallation,[15] in the copper-cycle the relative order of these two steps is uncertain, thus either of the two routes of Fig. 2 can take place. Most recent reports favour the mechanism in which the nucleophile reacts with the copper(I) halide catalyst before the oxidative addition.

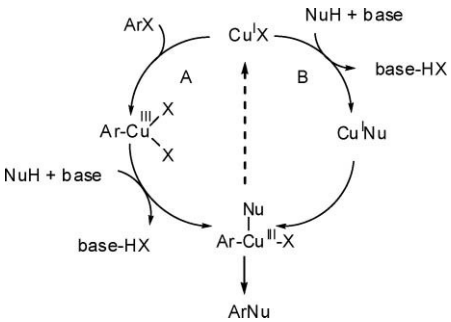


Fig. 1 Two possible pathways for the relative order of the oxidative addition and the transmetallation steps in the Cu(I)/Cu(III) mechanism.

2.1.2. Mechanistic pathways involving single electron transfer (SET). In 1937, Waters was probably one of the first to propose that free-radicals could be involved in the Ullmann reaction, but at that time this was just speculation.[78–80] In the 60's, an electron transfer radical mechanism for aliphatic nucleophilic substitution was proposed by two authors, Kornblum[81] and Russell,[82] who independently were working on chain reactions *via* radical anion intermediates. Bunnett extensively studied radical nucleophilic substitution reactions and expanded these studies to aromatic systems.[83–90] In his first report,[83] he investigated the reactivity of various 5- and 6-halopseudocumenes with KNH_2 in liquid ammonia, expecting the reaction to proceed *via* an aryne intermediate and through a rearranging substitution mechanism. Instead, based on the product ratio, he concluded that a

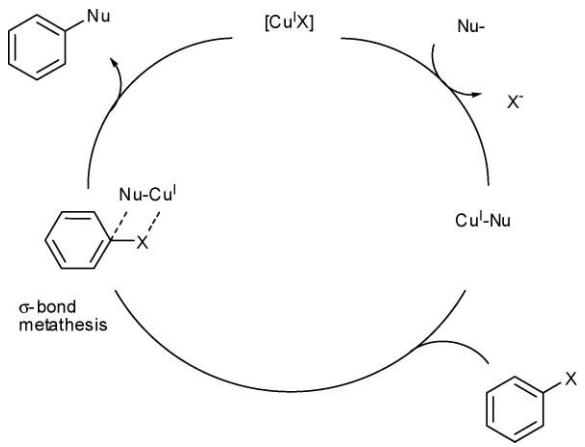


Fig. 2 Proposed catalytic cycle involving an intermediate *via* σ-bond metathesis.

non-rearranging substitution mechanism was clearly in competition with the aryne mechanism. After performing some tests in the presence of a radical scavenger (tetraphenylhydrazine) he was finally convinced of the formation of aryl halide radical anions in the mechanistic cycle. He then proposed the designation '$S_{RN}1$' for this type of mechanism, which stands for unimolecular radical-nucleophilic substitution; this notation is still in use. In general terms, the $S_{RN}1$ mechanism is a chain reaction mechanism, and as such comprises of initiation, propagation and termination steps (Scheme 4).

(1) $(ArX)^{\bullet -} \rightarrow Ar^{\bullet} + X^-$

(2) $Ar^{\bullet} + Nu^- \rightarrow (ArNu)^{\bullet -}$

(3) $(ArNu)^{\bullet -} + ArX \rightarrow ArNu + (ArX)^{\bullet -}$

Scheme 4 General scheme for the $S_{RN}1$ mechanism.

In the initiation step, an electron is added to a suitable substrate by one of several procedures, such as photochemically, electrochemically, by redox agents, by added solvated electrons, or thermally.[91] The radical anion then undergoes fragmentation into an aryl radical and the anion of the leaving group.[92] Subsequently, the aryl radical couples with the nucleophile, forming a new radical anion, which eventually transfers its electron to the substrate. Summation of these three steps provides the overall equation: $ArX + Nu^- \rightarrow ArNu + X^-$, which accounts for an aromatic nucleophilic substitution that involves radical and radical anion intermediates and an electron transfer step.

Since it was already known that metals and organometallic compounds that are capable of electron transfer[71,93–95] also catalyze aromatic nucleophilic substitution,[96] the step to connect the copper-catalyzed Ullmann reaction to the $S_{RN}1$ mechanism was a plausible one.

An important study was reported in 1978 by Arai *et al.* on the reaction of 1-bromoanthraquinone (AQBr) with 2-aminoethanol (AE), catalyzed by CuBr in a mixture of 1,2-dimethoxyethane and methyl cellosolve as solvent.[96–98] Using EPR experiments they could demonstrate the formation of an organic paramagnetic species, identified as 1-bromoanthraquinone radical anion ($AQBr^{\bullet -}$) derived by an electron transfer from the Cu(I) species to 1-bromoanthraquinone ($AQBr + Cu(I) \rightarrow AQBr^{\bullet -} + Cu(II)$). In the reaction system, anthraquinone (AQH) was also produced, and its formation was explained again *via* the formation of the $AQBr^{\bullet -}$ radical anion, by its dehalogenation process ($AQBr^{\bullet -} \rightarrow AQ^{\bullet} \rightarrow AQH$). This was the first time the formation of an organic radical was observed as a result of the oxidation of Cu(I) to Cu(II). This and other reports[99,100] supported the proposal that the copper-catalyzed aromatic nucleophilic substitution could follow a $S_{RN}1$ pathway.

Different proposals appeared in the literature, mainly thanks to major contributions of Kochi to the field.[100,101] Since he showed that a free radical reacts rapidly with a Cu(II) species *via* atom transfer (Scheme 6, eqn (2–3)) another pathway could be possible, depicted as follows (Scheme 5):

(1) $ArX + Cu(I)X \rightarrow Ar^{\bullet} + Cu(II)X_2$

(2) $Ar^{\bullet} + Nu- \rightarrow (ArNu)^{\bullet -}$

(3) $(ArNu)^{\bullet -} + Cu(II)X_2 \rightarrow ArNu + Cu(I) + X^-$

Scheme 5 General scheme for copper-catalyzed $S_{RN}1$-type mechanism for the Ullmann coupling.

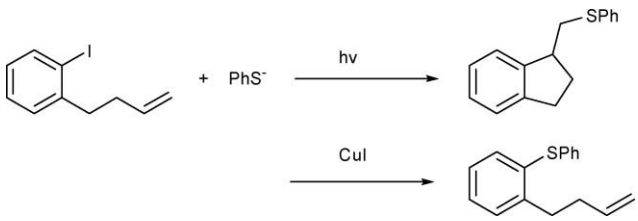
(1) $Cu(I)X + Nu^- \rightarrow Cu(I)Nu + X^-$

(2) $ArX + Cu(I)Nu \rightarrow Ar^{\bullet} + Cu(II)XNu$

(3) $Ar^{\bullet} + Cu(II)XNu \rightarrow ArNu + Cu(I)X$

Scheme 6 Halogen atom transfer $S_{RN}1$-type mechanism.

Despite the several investigations which supported an aryl halide activation *via* the Cu(I)/Cu(II) redox couple (SET), other authors reported evidence against such a radical mechanism.[57,73,74] In particular, Bowman performed two diagnostic tests to disprove the involvement of $S_{RN}1$-type mechanism for a C–S coupling, comparing the results obtained for this reaction, when it was either initiated by photostimulation or catalyzed by copper iodide.[76] In the first test, he used 1-chloro-4-iodobenzene, which was reacted with phenylthiolate. Under $S_{RN}1$ conditions (photostimulated), the only product was the disubstituted product. When the reaction was repeated in the presence of catalytic CuI, exclusively mono-substituted product was obtained. The results clearly indicated a difference in operating mechanism for the two reactions. However, our view is that whereas the use of ultraviolet light can overcome the high energy barrier, necessary for the breakage of a C–Cl bond, this energy barrier may simply be too high for the copper catalyzed reaction. The second test was based on the potential intramolecular ring closure between an olefin and an aryl radical to prove the presence of aryl radical intermediates (Scheme 7). The copper-catalyzed reaction yielded solely the coupled product and no cyclisation product was observed, whereas the reaction under $S_{RN}1$ conditions gave the cyclisation product.

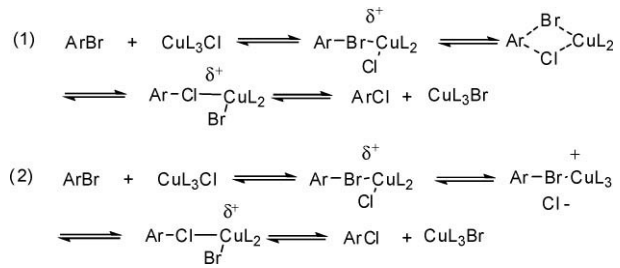


Scheme 7 Radical clock test for the presence of aryl radicals.

Therefore, the absence of ring closure in the copper-catalyzed reaction provided evidence against aryl radicals as intermediates.

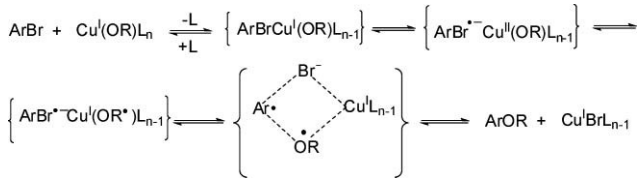
Here it should be noted that the validity of using this radical-clock type experiment in the presence of transition metal catalysts has not been proven.[102] Whereas in the light-stimulated experiment the competition is between ring-closure and reaction with the thiolate anion, in the copper-catalyzed reaction the competition is between ring-closure and reaction with the copper thiolate complex, which is still in very close proximity to the aryl radical. Hence, this latter reaction may be much faster than ring-closure.

2.1.3 Mechanistic pathways involving σ-bond metathesis. In this reaction type, the copper catalyst is assumed not to change its oxidation state during the cycle, remaining in its +1 state. One of the proposals involves the activation of the aryl halide *via* a four-centred intermediate between the aryl halide and the copper catalyst. The metal catalyst is proposed to form a σ-complex with the lone electron pair of the halogen atom, thus inducing polarisation of the carbon-halogen bond that facilitates the subsequent attack by the nucleophile. In the course of their studies on substitution reactions between aryl halides and cuprous salts, Bacon and Hill used this mechanism to explain their results (Scheme 8, eqn (1)).[103–105]



Scheme 8 Bacon's proposals for reaction intermediates.

However, multi-centre processes are not easy to differentiate from those involving an ionic intermediate (Scheme 8, eqn (2)), and thus such a mechanism is hard to ascertain. Litvak and Shein investigated the mechanism of the copper catalysed reaction of aryl bromides with sodium methoxide and they proposed a mechanism in which they combined a radical process with a four-centre intermediate (Scheme 9).[106] A few years later though, van Koten and co-workers systematically studied the copper-catalyzed reaction of sodium methoxide with aryl halides,[59] and reported an alternative mechanism for the same reaction, *via* intimate-electron transfer, through the Cu(I)–Cu(II) redox couple.

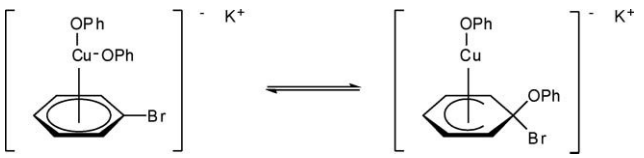


Scheme 9 Litvak and Shein's proposal for the copper-catalyzed etherification reaction.

In a general overview of these proposals, a potential scheme for the mechanistic pathway *via* σ-bond metathesis can be depicted as in Fig. 2.

The first step in this cycle is the displacement of the halide by the nucleophile, to form a Cu–Nu species which acts as the catalyst for the coupling reaction. Subsequently, the copper catalyst coordinates to the aryl halide *via* a four-centred intermediate, in which the coordination is orientated by the partial charges on Cu^+ and on the electronegative halide, respectively. Therefore, the polarisation of the C–X bond creates a partial positive charge on the *ipso*-carbon and assists the substitution by the nucleophile, to give the coupling product and the free Cu(I) species.

2.1.4 Mechanistic pathways involving π-complexation. In 1964 Weingarten not only reported evidence for the catalytic activity of a copper(I) species, but he also proposed a new mechanism for the aryl halide activation step.[57] The reaction that was investigated by a kinetic study, concerned the formation of phenyl ether from bromobenzene and potassium phenoxide. In this Ullmann coupling, the typical reactivity pattern of aryl halides for the nucleophilic aromatic substitutions was observed and in particular it was found that the relative reactivities of different aryl halides (ArI > ArBr > ArI) parallels the one observed for reactions known to involve a C–X (X = halogen) bond cleavage step.[107] Thus, it was proposed that the catalyst activated the aryl halide through the interaction of the copper(I) species with the π-electrons of the aromatic system. The intermediate that was proposed to be part of the catalytic reaction looked as depicted in Scheme 10, in which the metal functions as an electron sink and assists the replacement of the halogen by the nucleophile. In addition, the copper complexation leads to stabilization of the Wheland complex.



Scheme 10 Weingarten's proposal for the intermediate *via* π-complexation in the reaction of bromobenzene and potassium phenoxide.

This proposal was supported to some extent by the known structures of Cu(I)-benzene complexes,[108,52] although these tend to be η^2-complexes, and by the similarities seen with the already studied chlorobenzene-chromium tricarbonyl complexes, found to be reactive in nucleophilic aromatic substitution.[109] This mechanistic pathway has been proposed several times but attracted neither large support nor disagreement.[61] Calculations have shown that η-6 coordination is preferred over η-2 or η-1 coordination in complexes between copper(I) and benzene.[110] However, in practice η-6 complexes are rare.[111]

We can summarize this proposal by the catalytic cycle in fig. 3. In this mechanism, in which the copper species maintains its +1 oxidation state, there is prior coordination of the copper catalyst to the aromatic ring. The aryl halide then undergoes a polarization which facilitates the substitution of the halide on the ring and brings about the formation of a copper-product complex. Release of the coupling product restores the copper(I) catalyst.

3. Recent mechanistic investigations on the modified Ullmann reaction

As discussed in the introduction, the Ullmann condensation has been much improved through the addition of ligands, which enabled faster reactions and allowed milder conditions. This

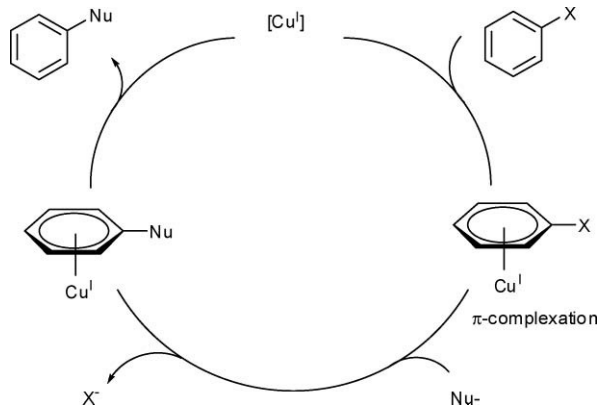


Fig. 3 Proposed catalytic cycle involving an intermediate *via* π-complexation.

effect has initially been explained through improved solubility and stability of the active copper species.[112] The development of these new catalytic protocols and the screening of various ligands/additives have already been the subject of many excellent reviews.[19–26] Relatively few studies were dedicated to mechanistic investigations on the actual role of the ligand and/or on a possible catalytic cycle.

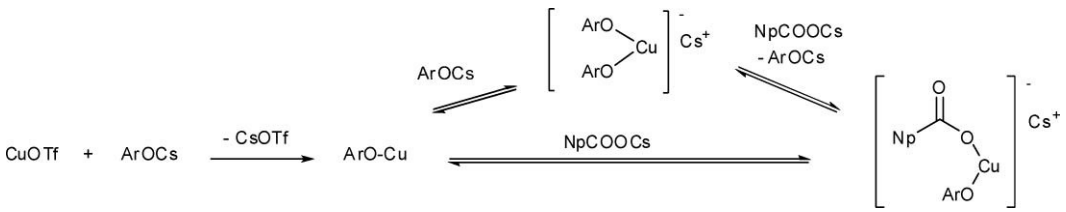
In an early publication on the synthesis of diaryl ethers for example, Buchwald found that stoichiometric quantities of carboxylic acids promoted the coupling of less reactive phenols with aryl bromides and iodides.[113] Together with the caesium carbonate used as a base, the additives appeared to increase the solubility of the intermediates, allowing to perform the reaction also with less soluble phenols and phenols containing electron-withdrawing groups (Scheme 11). Liebeskind and co-workers introduced the use of Cu(I) 2-thiophenecarboxylate (CuTC) as soluble and highly active catalyst for the reductive Ullmann coupling.[114]

More recently, Taillefer, Jutand and co-workers conducted a structure/activity relationship study on the diaryl ether formation catalyzed by CuI with *N*,*N*-chelating ligands.[115] They found that the best performing ligands contain an imine- and a pyridine-binding site and she investigated the influence of the electron density of the binding sites on the reactivity of the catalyst in the arylation of 3,5-dimethylphenol with iodobenzene. The results obtained were then explained by the authors using a cycle *via* an oxidative addition/reductive elimination mechanism (Scheme 12).

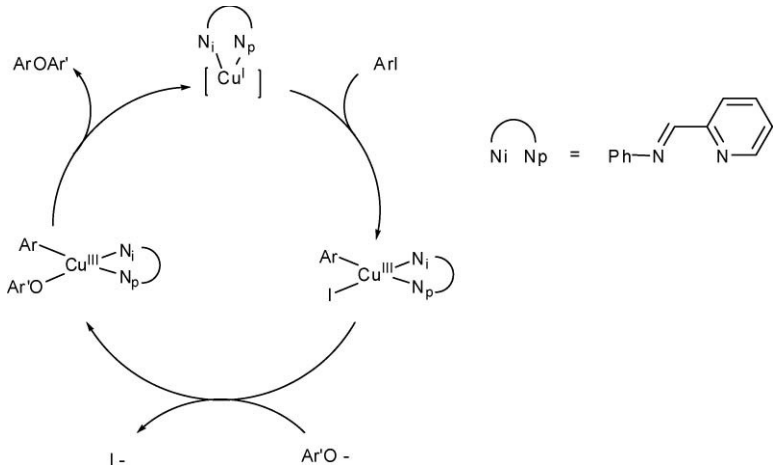
In another recent report, Taillefer investigated the role of a tetradentate N-ligand used for the C–O coupling and pointed out its influence on the solubility and the electronic properties of the copper centre.[44] In addition, he rationalized the role of the solvent acetonitrile in the early stages of the reaction, and concluded that acetonitrile coordination facilitates ligand exchange at the copper centre.

New publications have also appeared on the thiol arylation reaction.[19–26,116] Most authors propose an oxidative addition mechanism, mainly to account for the relative reactivities of electron-rich and electron-poor aryl halides (Scheme 13).[117,118]

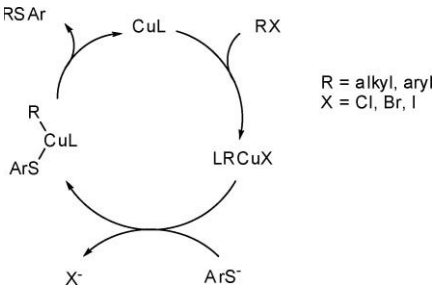
Most mechanistic research, however, has been focused on the C–N coupling reaction. Ma was the first to show that α-amino acids, acting as *N*,*O*-bidentate ligands for the metal can be arylated very fast at mild reaction temperatures.[25,119] He explained this accelerating effect by a mechanistic proposal which involves chelation of the amino acid to the copper ion, π-complexation of the copper to the aryl ring, and an intramolecular nucleophilic substitution step to form the coupling product ArNu (Scheme 14). This mechanistic scheme was used to account for the substituent effects of aryl halides but did not fully explain the reactivity order



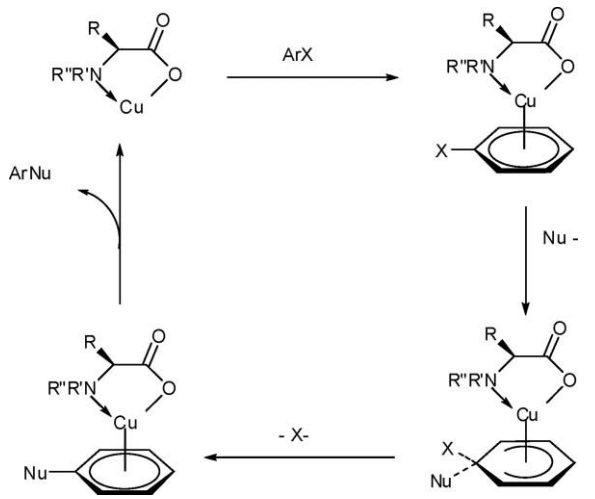
Scheme 11 Buchwald's mechanistic proposal for the effect of carboxylates in the synthesis of diaryl ethers.



Scheme 12 Jutand's mechanistic proposal for the synthesis of diaryl ethers.



Scheme 13 Mechanistic proposal for the synthesis of aryl thioethers.

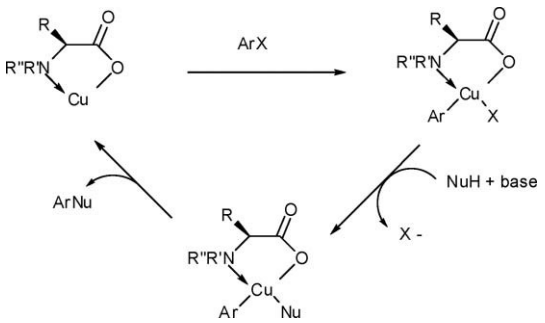


Scheme 14 Ma's mechanistic proposal for the coupling of aryl halides with α-amino acids.

found, *i.e.* ArI > ArBr > ArCl. No evidence was given for the π-complexation step.

Afterwards, Ma demonstrated that amino acids are suitable ligands for a variety of Ullmann type reactions, such as the coupling of aryl halides with primary amines, secondary cyclic amines and N-containing heterocycles.[25,120] Besides the previous proposal (Scheme 14), he suggested another catalytic cycle (Scheme 15), in which the chelation of Cu(I) with an α-amino acid makes the Cu(I) species more reactive toward an oxidative addition step and/or stabilizes the following intermediates, facilitating the coupling reaction.

This mechanism was used to explain the observed order I > Br > Cl for the ease of halogen displacement from the aromatic ring and the better reactivity shown by electron-deficient aryl halides. Fu and co-workers referred to the same mechanistic proposal for their catalytic protocol, which involved pipecolinic acid as ligand which could act as the α-amino acids in Ma's system.[121] Other reports using similar catalytic protocols with *N*,*O*- or *O*,*O*-

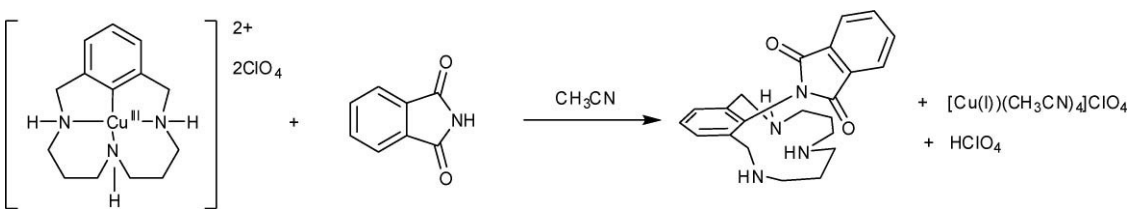


Scheme 15 Mechanistic proposal for the coupling reaction with amino acids as ligands.

bidentate ligands evoked the same mechanistic interpretation *via* oxidative addition/reductive elimination process.[122–124]

In 2004, Taillefer[125,126] reported a catalytic protocol for *N*- and *C*-arylations with aryl bromides and iodides. A range of chelating *N*,*N*- and *N*,*O*-ligands were screened in the arylation reactions with azoles, amides and malonic acid derivatives. Moreover, some mechanistic considerations for the *N*-arylation reaction were reported, starting by considering two possible mechanisms, involving radical intermediates or oxidative addition/reductive elimination steps. The presence of any kind of radicals was excluded on the basis of a number of experiments. First, inhibition of the coupling reaction upon use of radical scavengers or electron acceptors did not occur. Secondly, the test which was developed earlier by Bowman[76,83,86,88] was performed, using 1,4-diiodobenzene and pyrazole as substrates, and since only mono-substituted product was obtained, the hypothesis of the intermediacy of an aryl radical was rejected (*vide supra*). Thus, an oxidative addition/reductive elimination catalytic cycle was proposed, which could account for the experimental observations such as: (i) the reactivity order (ArI > ArBr ≫ ArCl) parallels the leaving group ability of halides; (ii) couplings are slightly favoured with electron-withdrawing groups on the aryl halide and disfavoured with electron-donating groups; (iii) steric hindrance on the substrates decreases the reaction rate. However, the authors underlined that uncertainty still remains on the relative order of the two steps, nucleophilic substitution and oxidative addition.[127] In other literature reports the same mechanistic proposal through a Cu(I)/Cu(III) cycle was suggested,[128–131] based mainly on similarities with previous reported reactions but without providing mechanistic evidence.

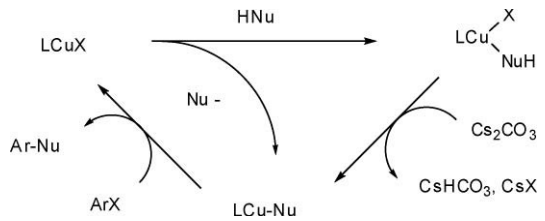
Stahl reacted an isolated Cu(III) macrocyclic pincer complex with acidic nitrogen compounds such as imides and was able to isolate the macrocyclic imide and a copper(I) complex (Scheme 16).[65] The reaction proceeds fairly rapidly without the addition of a base, testifying to the high reactivity of the Cu(III) complex. This



Scheme 16 Stahl's reaction of nitrogen nucleophiles on a Cu(III) macrocyclic pincer complex.[65]

result strongly suggests that the mechanism proceeds *via* reductive elimination of an aryl copper imidate complex. However, based on the available information a direct attack on the *ipso* carbon by the nucleophile could not be excluded.

Buchwald reported an interesting study on the *N*- and *O*-arylation of amino alcohols. He investigated the orthogonal selectivity that results by switching between to different ligands: a β-diketone or tetramethylphenanthroline, an N–N type ligand.[132] The mechanistic hypothesis was based on the two initial steps, which are considered responsible for the observed selectivities (Scheme 17).



Scheme 17 Buchwald's mechanistic hypothesis for the arylation of amino alcohols.

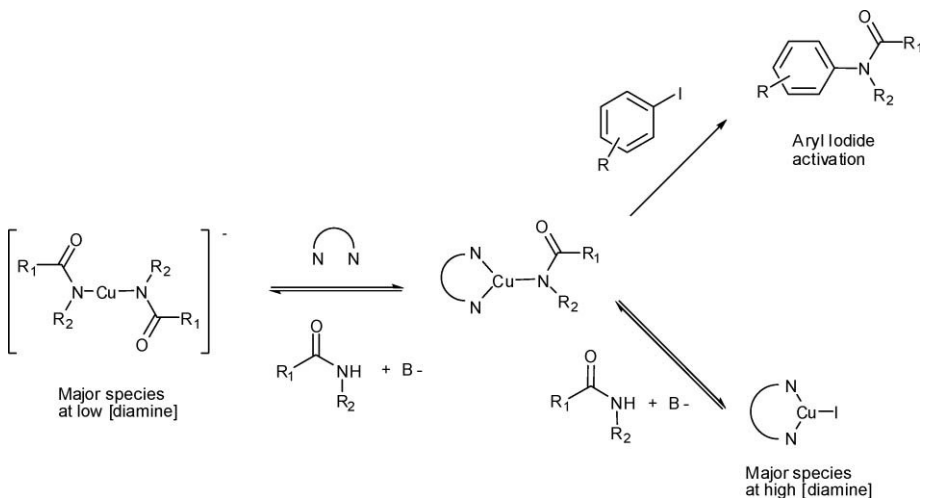
With this mechanistic scheme he could explain his observations, related to the electrophilicity of the ligated Cu-centre, *i.e.* the Cu(I)-diketone complex has a lower electrophilicity than the Cu(I)-tetramethylphenanthroline complex. Thus, in case of coordination with a diketone-ligand, this lower electrophilicity of the copper-centre would disfavour the binding of the alcohol and favour the amine to bind to Cu(I). In the case of the complexation of copper with the tetramethyl-phenanthroline ligand though, the coordination to the metal centre would lead to a more Lewis acidic copper species and would facilitate the formation of the copper-alcohol bond. Thus, in this mechanistic cycle there is a plausible explanation for why the coordination of the nucleophile should precede the transmetallation step, but the mode of aryl halide activation was not discussed. However, for a more detailed discussion of this phenomenon based on DFT calculations, see below.

Not only the copper-catalyzed *N*-arylation of amines was the subject of recent mechanistic study, but also the amidation reaction, the so-called Goldberg reaction, raised considerable interest.[133,134] In particular, Buchwald reported a kinetic study performed on the reaction between 3,5-dimethyliodobenzene and 2-pyrrolidinone, catalyzed by CuI in the presence of a chelating 1,2-diamine as ligand.[135,136] Through this study he identified the role of the diamine ligand in preventing multiple ligation of the amide. Indeed, at high concentration of the ligand the activation of the aryl halide becomes the rate-limiting step while, at low concentration of the diamine ligand, multiple ligation of the amide on copper occurs (Scheme 18). Thus, the dissociation of an amide and coordination of a diamine are required to generate the active copper species. Moreover, it was demonstrated that the copper(I)-amidate complex is an intermediate in the *N*-arylation process.

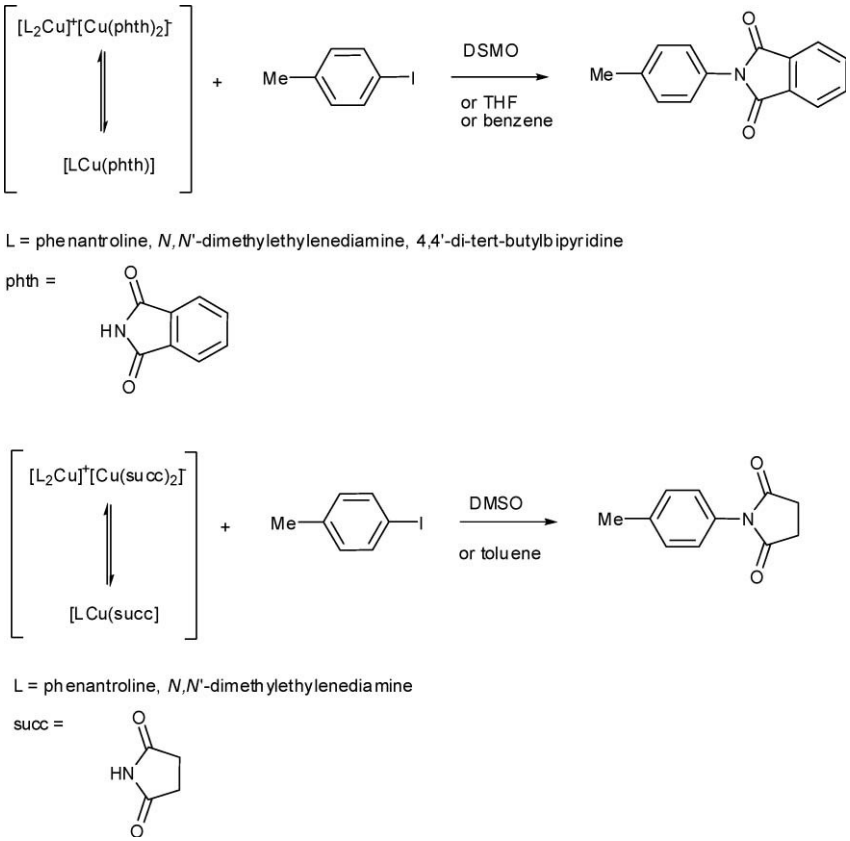
Three different mechanisms were considered for the reaction with the aryl halide: Cu(I)/Cu(III), SET and IAT. However, his data did not allow any choice between the three.

Buchwald's reports were among the ones that inspired a theoretical study on the copper-catalyzed Goldberg reaction. Guo and co-workers explored the reaction between phenyl bromide and acetamide *via* the density functional theory (DFT) method.[137] All the results were in good agreement with Buchwald's experimental observations and confirmed that the diamine-ligated copper(I) amidate is the most reactive intermediate in the reaction mixture, when compared to other possible copper(I) intermediate (*i.e.* cationic diamine-ligated Cu(I) or multiple amide-ligated Cu(I) complexes). In addition, the DFT calculations pointed to the oxidative addition of ArX on $L_2Cu(I)$-amidate as the rate-limiting step, to generate a $L_2Cu(III)$-(Ar)(X)(amidate) pentacoordinated species. However, this computational study considered only a mechanism based on oxidative addition/reductive elimination steps and neglected to evaluate the pathways for a possible electron-transfer mechanism.[127]

Hartwig and co-workers recently reported a detailed investigation about the possible reaction steps in the stoichiometric Goldberg reaction of haloarenes with *N*,*N*- or *P*,*P*-ligated copper complexes containing anionic nitrogen ligands.[138] In this work, they described the synthesis and characterisation of the copper



Scheme 18 Buchwald's proposed mechanism for the Goldberg reaction using a Cu(I)-catalyst with diamine ligands.



Scheme 19 Reactions with isolated copper complexes studied by Hartwig.[138]

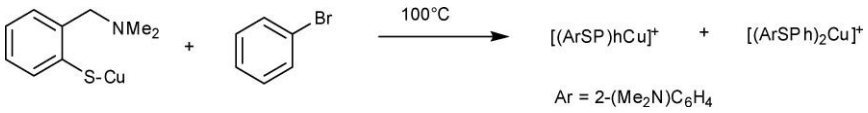
amidate and imidate complexes (Scheme 19), and they obtained kinetic data on the reactions of these species with haloarenes. In particular, the rates of the reactions with *p*-cyano-chlorobenzene and 1-bromonaphthalene were compared. These compounds have similar reduction potentials and similar rates of halide dissociation from the radical anions. Thus if the reactions proceed by a radical mechanism the rates with these two substrates should be similar. In practice the chloro-compound did not react but rather decomposed, whereas the bromo-naphthalene was converted in high yield. This argues against a radical mechanism. The kinetic data were supported with DFT calculations. The authors provided rate and mechanistic data about the possible individual steps of the C–N coupling process. The neutral ligated copper imidate and amidate complexes are subject to a disproportionation equilibrium in which two eq. of the neutral complex form one equiv. of $[L_2Cu]^+[Cu(amidate)_2]^-$. It is less likely that this anionic form is responsible for the amidation reaction as they were able to show that $R_4N^+Cu^I(phthalimidate)_2^-$ was not capable of reaction with an aryl bromide or iodide.

The intermediacy of free aryl radicals during the reaction could be excluded, based on a number of observations. First of all, he did not observe significant quantities of biaryl or arene-H products from the reactions of copper amidate/imidate complexes in solvents that can act as H-atom donors. Furthermore, studies on the effect of the electronic properties of the haloarene, in particular the lack of reaction of electron-poor chloroarenes and the high-yield reactions of more electron-rich bromoarenes, argued against pathways involving outer-sphere electron transfer to form haloarene radical anions. In addition, reactions of aryl iodides containing a radical clock ruled out the generation of free aryl radicals. On the other hand, arylcopper(III) intermediates containing dative nitrogen ligands were calculated to be kinetically accessible under mild conditions, and such species could be formed by a concerted oxidative addition or by an internal electron transfer and formation of an arylcopper species within the coordination sphere of the metal. Thus, Hartwig concluded that the Cu(I)/Cu(III) mechanism was the most likely one.

Similar research was performed by Hartwig on the phenol arylation reaction using pre-formed copper phenoxide complexes. Here also the same disproportionation occurs as in the case of the amidate and imidate complexes. Conductivity measurements showed that in solution, the complexes are predominantly present as $L_2Cu^+Cu(OPh)_2^-$. In this case $R_4N^+Cu^-(OPh)_2$ did react slowly with iodobenzene to give a meagre 10% yield of PhOPh whereas use of $L_2Cu^+Cu(OPh)_2^-$ led to clean and high yielding reactions. This again seems to prove the idea that it is the neutral LCu(OPh) that is the reactive catalyst. Radical clock experiments tested negative for radicals.[139]

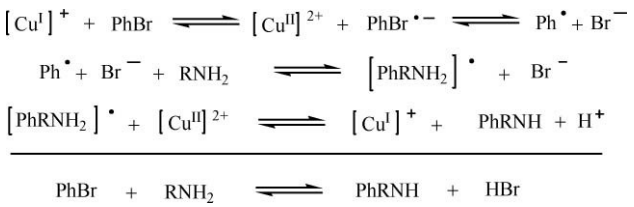
Van Koten and co-workers reported the catalytic activity of an aminoarenethiolato-copper(I) complex, CuSAr, in the reaction of benzylamine with bromobenzene.[140] CuSAr is acting as a pre-catalyst and is converted in the initial stages of the reaction into CuBr/PhSAr which presumably is the actual active catalytic system (Scheme 20).

The catalyst was capable of catalysing the arylation of amines. Kinetics showed that the reaction is first order in catalyst, aryl halide and amine. Surprisingly, in these reactions aryl bromides reacted much faster than the iodides. The authors showed that the



Scheme 20 Active catalyst in van Koten's amination.

use of radical traps slowed down or stopped the C–N coupling reaction. These and other observations on the reactivity of the system employed, like the activating effect of the addition of metallic copper to the reaction mixture and the observation of a parallel oxidation process for the benzylamine used, led the authors to propose a mechanism for this reaction (Scheme 21), which involves a single-electron transfer (SET) from the Cu(I) centre to the aryl bromide to form an aryl radical (kinetically protected by the back reaction with Cu(II)) and a Cu(II) species, subsequent reaction with the amine partner and a second SET to regenerate the Cu(I) species.

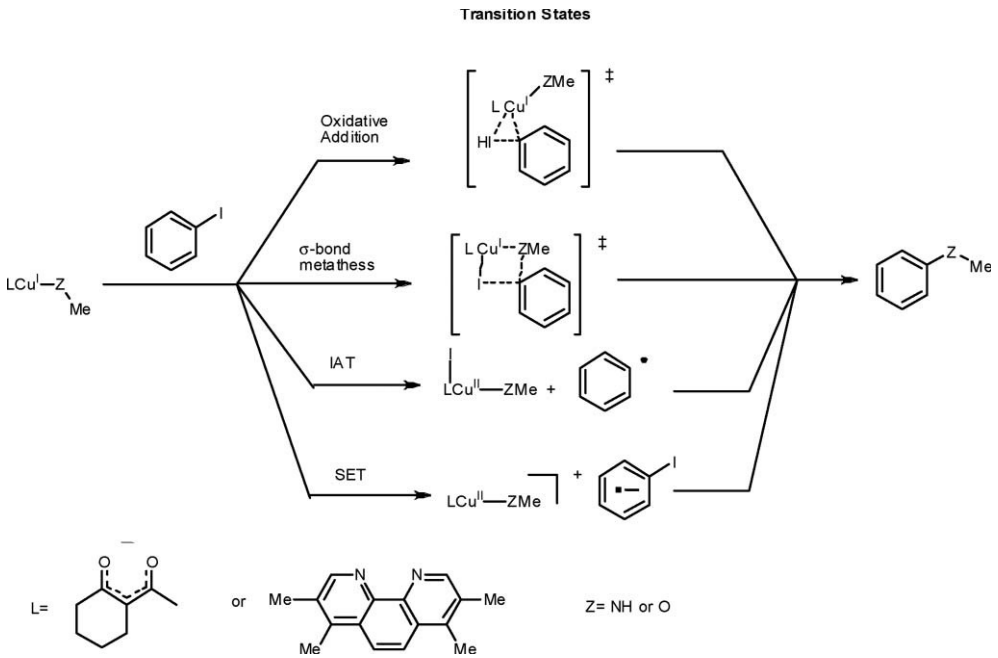


Scheme 21 Mechanistic proposal for aminoarenethiolato-copper(I) catalyzed amination of bromobenzene.

In this type of reaction a build-up of Cu(II) can occur either as a result of scavenging of the aryl radical, or due to the disproportionation mechanism. This results in a slower reaction rate as a result of the lack of Cu(I). Indeed, experimentally these reactions were found to slow down considerably over time. Addition of copper powder restored the Cu(I) levels as a result of the comproportionation reaction between Cu(0) and Cu(II) and was found to improve the rate of the reaction leading to full conversions. Although this mechanistic proposal is based on the study of one single model reaction, it is a clear example of the involvement of a radical pathway.

A recent comprehensive study from Houk, Buchwald and co-workers used DFT calculations to discriminate between four different mechanisms (Scheme 22).[141]

They studied the reactions between iodobenzene and both methanol and methylamine as a previous study (*vide supra*) had shown that the *O- vs. N*-selectivity of the arylation of aminoethanols depended upon the nature of the ligand, which was either of the diketone type or a phenanthroline. The outcome of the DFT calculations showed that formation of the Cu(I) methoxide complex is easier than formation of the amide complex. However, the rate determining step is the reaction with the aryl iodide. This step was calculated for both ligand types and nucleophiles for all four mechanisms (Table 1). From the results it is clear that when phenanthroline is used as a ligand the IAT and SET mechanisms have similar barriers and either may occur depending on the nucleophile. The copper catalysed *O*-arylation reaction proceeds *via* IAT, whilst the *N*-arylation proceeds *via* SET. In the arylations with the diketone ligand, both reactions favour the SET mechanism. Significantly, the oxidative addition could be excluded based on the unfavourable TS.



Scheme 22 Four mechanisms explored using DFT calculations.

Table 1 Free energies (kcal mol^{-1}) for TS and other key stationary points in ligand promoted *O*- and *N*-arylation reactions

Nucleophile	Ligand	CuZMe formation	TS OA	TS Sig	TS IAT	TS SET	Product formation
MeO	Diketone	2.9	64.6	57.1	32.9	27.2	–41.3
MeNH	Diketone	14.8	55.0	65.6	41.1	26.2	–48.0
MeO	Phenanthroline	7.2	43.2	43.4	34.0	43.6	–47.1
MeNH	Phenanthroline	17.0	53.7	50.9	39.6	35.1	–52.6

Summary and outlook

The question remains if there really is a single mechanism for all copper catalysed *N*-and *O*-arylations. Nevertheless, major progress has been made in unravelling the mechanism of the modified Ullmann reaction, particularly in the last few years. By now, most authors agree that reaction between the copper precursor complex and the nucleophile precedes the activation of the aryl halide. Indeed, the electron-rich copper alkoxide or amide complex is much more reactive than the copper halide, regardless of what the second step of the mechanism is.

Thus far it would seem that the mechanism of the aryl halide activation may differ depending on the halide, the ligand and the nucleophile. Involvement of radical intermediates, although proposed by many authors, was initially discounted based on competition experiments and radical clock experiments. However, the validity of both types of experiments in this context is at least open to questioning. The radical clock test is based on the occurrence of very rapid follow-on reactions of the formed aryl radical, such as ring-opening or closing, a valid type of proof in organic chemistry, where most reaction rates have been charted out much earlier. Here we are dealing with organometallic reactions for which little is known on the rate of the individual steps, in particular of the radical type. Recent work from van Koten and co-workers and Buchwald and Houk and co-workers provide compelling evidence for a radical type mechanism in the reaction between the copper-nucleophile complex and the aryl halide. Nevertheless, research by Buchwald, Hartwig, Stahl and others on the Goldberg reaction and on the phenol arylation seem to provide strong evidence against a radical mechanism and here the Cu(I)/Cu(III) mechanism may be operative.

Increasingly, DFT calculations are used to distinguish between pathways. However, it should be stressed that the value of this method lies in its ability to compare different mechanisms. Thus, all possible mechanisms should be calculated in order to make a meaningful comparison. The Buchwald–Houk study described above is a very good example and more studies are expected in the future.

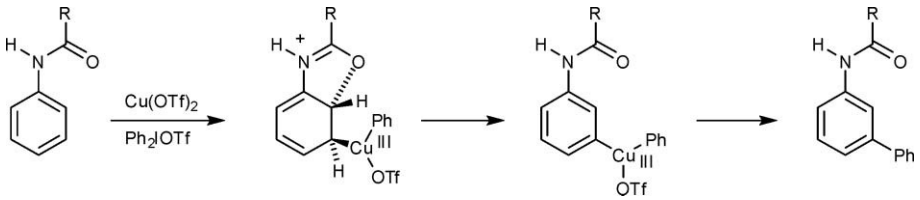
The question remains if the mechanisms described in this paper are the final word. In this respect, the recent findings of both Bolm and Buchwald[142] as well as Norrby and Bolm and co-workers[143] on the use of "homeopathic doses" of copper oxide (both Cu_2O as well as CuO were used) in the copper catalysed arylation of a range of nitrogen nucleophiles still evokes a number of questions. In these reactions a very large excess of ligand still needs to be used. The suggestion is that in reactions with larger amounts of copper the majority of copper is not involved in the catalytic cycle but parked in some form of resting state. A possible explanation could be that the copper is present in the form of nanoparticles. It is by now well accepted that high temperature Heck–Mizoroki reactions proceed *via* the formation of palladium nanoparticles.[144–146] Use of high substrate catalyst ratios leads to the formation of very small nanoparticles as the reaction with the aryl halide solubilises the palladium in the form of monomeric anionic complexes. This "eating away" at the rim of the nanoparticles counters the natural tendency of the nanoparticles to increase in size, the so-called Oswald ripening. If the substrate/catalyst ratio is too low, the Ostwald ripening wins, the nanoparticles become too big, most of the palladium atoms are inside the nanoparticles and hence inactive and finally palladium will precipitate as palladium black. Thus, the higher the S C^{-1} ratio the higher the turnover frequency will be.[147] Both Cu(0) as well as Cu(I) and Cu(II) oxide can form nanoparticles. Moreover, as in most reactions halide anions, either from the substrate or from the used copper salt precursor, are abundant, even under apparently homogeneous reaction conditions, the presence of nano-particles of copper halide salts (copper in various oxidation states with bridging halides, *cf.* ref. 68) could be anticipated. The tendency of many (mixed valence) copper salt complexes to exist at least in the solid state as sometimes highly aggregated species (as determined by X-ray structure determination techniques) has been extensively documented. An EXAFS and/or TEM study could reveal the presence of such nanoparticles.

Thus, in conclusion, although much progress has been made in unravelling the mechanism of the modified Ullmann reaction, much remains to be uncovered.

Finally, looking into the future one may wonder if the mechanisms of the recently discovered copper-catalysed C–H activation reactions shows any similarity with those discussed here.[148–150] In this respect, the work of Ribas, Stahl and co-workers is highly intriguing.[151] They studied in detail the formation of a cationic $[ArCu(III)Br]^+Br^-$ complex in which the ArH is part of a triaza macrocycle *via* reaction between ArH and $Cu(II)Br_2$ (See also Scheme 16). In the first step of their proposed mechanism a coordination complex is formed between the macrocycle and $CuBr_2$. In the next step a disproportionative cupration of ArH happens in which simultaneously the ArCu(III) complex is formed and a second molecule of $Cu(II)Br_2$ is reduced to Cu(I)Br. This cupration was made part of a catalytic cycle by the addition of a nucleophile and oxygen as oxidant. Thus ArOMe was formed in the presence of MeOH and O_2. The reaction with MeOH is proposed to lead to the $[ArCu(III)OMe]^+Br^-$ complex, which has also been proposed as intermediate in the modified Ullmann couplings discussed above.

Gaunt recently showed that treatment of anilides with catalytic $Cu(OTf)_2$ and Ph_2IOTf resulted in *meta*-arylation of acetanilide.[152] They propose a mechanism *via* dearomatising cupration, involving a Cu(III) species (Scheme 23).

Many new developments can be expected in this area.



Scheme 23 Gaunt's proposed mechanism for the copper-catalyzed *ortho*-arylation.

Acknowledgements

We thank the Dutch Ministry of Economic Affairs, NWO/CW, DSM, Organon N.V. and Solvay Pharmaceuticals for financial support administered through the CW/CombiChem programme. We are grateful to Dr B. de Lange (DSM, The Netherlands) and to Prof. H. J. Heeres (University of Groningen, The Netherlands) for their help and the useful discussions.

References

1 F. Ullmann, *Ber. Dtsch. Chem. Ges.*, 1903, **36**, 2382.
2 F. Ullmann, *Ber. Dtsch. Chem. Ges.*, 1904, **37**, 853.
3 I. Goldberg, *Ber. Dtsch. Chem. Ges.*, 1906, **39**, 1691.
4 P. N. Craig, in *Comprehensive Medicinal Chemistry*, C. J. Drayton, Ed., Pergamon Press: New York, 1991, Vol. 8.
5 *Comprehensive Heterocyclic Chemistry II*, A. R. Katritzky, C. W. Rees, ed., Elsevier, Oxford, 1996.
6 J. B. Buckingham, *Dictionary of Natural Products*, CRC Press, 1994, Vol. 1.
7 G. D'Aprano, M. Leclerc, G. Zotti and G. Schiavon, *Chem. Mater.*, 1995, **7**, 33.
8 J. Hassan, M. Sévignon, C. Gozzi, E. Schulz and M. Lemaire, *Chem. Rev.*, 2002, **102**, 1359.
9 P. E. Fanta, *Chem. Rev.*, 1946, **38**, 139.
10 P. E. Fanta, *Chem. Rev.*, 1964, **64**, 613.
11 P. E. Fanta, *Synthesis*, 1974, 9.
12 A. A. Goldberg, *J. Chem. Soc.*, 1952, 4368.
13 W. R. H. Hurtley, *J. Chem. Soc.*, 1929, 1870.
14 J. F. Hartwig, *Modern Amination Methods*A. Ricci, Ed.; Wiley- VCH: Weinheim, Germany, 2000.
15 L. Jiang, S. L. Buchwald, in *Metal-Catalyzed Cross-Coupling Reactions*A. De Meijere, F. Diederich Eds,.; Wiley-VCH: Weinheim, 2004; Vol. 2, p 699.
16 A. F. Littke and G. C. Fu, *Angew. Chem., Int. Ed.*, 2002, **41**, 4176.
17 D. S. Surry and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2008, **47**, 6338.
18 E. M. Beccalli, G. Broggini, M. Martinelli and S. Sottocornola, *Chem. Rev.*, 2007, **107**, 5318.
19 I. P. Beletskaya and A. V. Cheprakov, *Coord. Chem. Rev.*, 2004, **248**, 2337.
20 S. V. Ley and A. W. Thomas, *Angew. Chem., Int. Ed.*, 2003, **42**, 5400.
21 K. Kunz, U. Scholz and D. Ganzer, *Synlett*, 2003, 2428.
22 J.-P. Finet, A. Y. Fedorov, S. Combes and G. Boyer, *Curr. Org. Chem.*, 2002, **6**, 597.
23 F. Monnier and M. Taillefer, *Angew. Chem., Int. Ed.*, 2008, **47**, 3096.
24 G. Evano, N. Blanchard and M. Toumi, *Chem. Rev.*, 2008, **108**, 3054.
25 D. Ma and Q. Cai, *Acc. Chem. Res.*, 2008, **41**, 1450.
26 F. Monnier and M. Taillefer, *Angew. Chem., Int. Ed.*, 2009, **48**, 6954.
27 A. Klapars, X. Huang and S. L. Buchwald, *J. Am. Chem. Soc.*, 2002, **124**, 7421.
28 J. C. Antilla, A. Klapars and S. L. Buchwald, *J. Am. Chem. Soc.*, 2002, **124**, 11684.
29 F. Y. Kwong and S. L. Buchwald, *Org. Lett.*, 2003, **5**, 793.
30 D. Ma, Q. Cai and H. Zhang, *Org. Lett.*, 2003, **5**, 2453.
31 W. Deng, Y. F. Wang, Y. Zou, L. Liu and Q. X. Guo, *Tetrahedron Lett.*, 2004, **45**, 2311.
32 H. B. Goodbrand and N.-X. Hu, *J. Org. Chem.*, 1999, **64**, 670.
33 R. Gujadhur, D. Venkataraman and J. T. Kintigh, *Tetrahedron Lett.*, 2001, **42**, 4791.
34 R. K. Gujadhur, C. G. Bates and D. Venkataraman, *Org. Lett.*, 2001, **3**, 4315.
35 M. Wolter, A. Klapars and S. L. Buchwald, *Org. Lett.*, 2001, **3**, 3803.
36 C. Han, R. Shen, S. Su and J. A. Porco, *Org. Lett.*, 2004, **6**, 27.
37 G. Evindar and R. A. Batey, *Org. Lett.*, 2003, **5**, 133.
38 F. Lang, D. Zewge, I. N. Houpis and R. P. Volante, *Tetrahedron Lett.*, 2001, **42**, 3251.
39 C. Enguehard, H. Allouchi, A. Gueiffier and S. L. Buchwald, *J. Org. Chem.*, 2003, **68**, 4367.
40 F. Y. Kwong, A. Klapars and S. L. Buchwald, *Org. Lett.*, 2002, **4**, 581.
41 P. J. Fagan, E. Hauptman, R. Shapiro and A. Casalnuovo, *J. Am. Chem. Soc.*, 2000, **122**, 5043.
42 B. de Lange, M. H. Lambers-Verstappen, L. Schmieder-van, de Vondervoort, N. Sereinig, R. de Rijk, A. H. M. de Vries and J. G. de Vries, *Synlett*, 2006, 3105.
43 A. Shafir and S. L. Buchwald, *J. Am. Chem. Soc.*, 2006, **128**, 8742.
44 A. Ouali, J-F. Spindler, A. Jutand and M. Taillefer, *Organometallics*, 2007, **26**, 65.
45 A. H. M. de Vries, J. G. de Vries, F. B. J. van Assema, B. de Lange, D. Mink, D. J. Hyett, P. J. D. Maas WO 2006/069799, to DSM IP Assets BV, 2006.
46 B. J. Hataway, *Coord. Chem. Rev.*, 1981, **35**, 211.
47 B. J. Hataway and D. E. Billing, *Coord. Chem. Rev.*, 1970, **5**, 143.
48 N. Krause, *Modern Organocopper Chemistry*, John Wiley&Sons, 2002, Chap. 1.
49 D. McIntosh and G. A. Ozin, *J. Am. Chem. Soc.*, 1976, **98**, 3167.
50 W. Levason and D. Spicer, *Coord. Chem. Rev.*, 1987, **76**, 45.
51 T. V. Popova and N. V. Aksenova, *Russ. J. Coord. Chem.*, 2003, **29**, 743.
52 F. A. Cotton, G. Wilkinson, C. A. Murillo, M. Bochmann, in *Advanced Inorganic Chemistry*, John Wiley&Sons, 1999, pp 854–876.
53 *Organometallic Compounds of Nickel, Palladium, Platinum, Copper, Silver and Gold*, R. J. Cross, D. M. P. Mingos, ed., Chapman and Hall, London, 1985.
54 P. J. Pérez, M. M. Díaz-Requejo, in *Comprehensive Orgamometallic Chemistry III*, R. Crabtree, M. Mingos, ed., Elsevier Science, 2006, Vol 2, K. Meyer, Volume ed. p153.
55 R. G. R. Bacon and H. A. O. Hill, *Q. Rev. Chem. Soc.*, 1965, **19**, 95.
56 P. E. Weston and H. Adkins, *J. Am. Chem. Soc.*, 1928, **50**, 859.
57 H. Weingarten, *J. Org. Chem.*, 1964, **29**, 3624.
58 A. J. Paine, *J. Am. Chem. Soc.*, 1987, **109**, 1496.
59 H. L. Aalten, G. van Koten, D. M. Grove, T. Kuilman, O. G. Piekstra, L. A. Hulsof and R. A. Sheldon, *Tetrahedron*, 1989, **45**, 5565.
60 M. Mansour, R. Giacovazzi, A. Ouali, M. Taillefer and A. Jutand, *Chem. Commun.*, 2008, 6051.
61 J. Lindley, *Tetrahedron*, 1984, **40**, 1433.
62 C. Couture and A. J. Paine, *Can. J. Chem.*, 1985, **63**, 111.
63 Note: with 'historical overview' we consider years between 1900's and 1980's.
64 Derek van Allen, PhD Thesis, 2004, University of Massachusetts Amherst.
65 L. M. Huffman and S. S. Stahl, *J. Am. Chem. Soc.*, 2008, **130**, 9196.
66 R. Xifra, X. Ribas, A. Llobet, A. Poater, M. Duran, M. Solà, T. D. P. Stack, J. Benet-Buchholz, B. Donnadieu, J. Mahía and T. Parella, *Chem.–Eur. J.*, 2005, **11**, 5146.
67 G. M. Whitesides, W. F. Fisher, J. San Filippo, R. W. Bashe and H. O. House, *J. Am. Chem. Soc.*, 1969, **91**, 4871.
68 G. M. Whitesides and P. E. Kendall, *J. Org. Chem.*, 1972, **37**, 3718.
69 C. R. Johnson and G. A. Dutra, *J. Am. Chem. Soc.*, 1973, **95**, 7783.
70 T. Cohen, J. Wood and A. G. Dietz, *Tetrahedron Lett.*, 1974, **15**, 3555.
71 G. van Koten, J. T. B. H. Jastrzebski and J. G. Nolte, *Tetrahedron Lett.*, 1976, **17**, 223.

72 G. van Koten, R. W. M. ten Hoedt and J. G. Noltes, *J. Org. Chem.*, 1977, **42**, 2705.
73 T. Cohen and I. Cristea, *J. Am. Chem. Soc.*, 1976, **98**, 748.
74 T. Cohen and I. Cristea, *J. Org. Chem.*, 1975, **40**, 3649.
75 D. Bethell and I. L. Jenkins, *J. Chem. Soc., Perkin Trans. 2*, 1985, 1789.
76 W. R. Bowman, H. Heaney and P. H. G. Smith, *Tetrahedron Lett.*, 1984, **25**, 5821.
77 T. P. Lockhart, *J. Am. Chem. Soc.*, 1983, **105**, 1940.
78 D. H. Hey and W. A. Waters, *Chem. Rev.*, 1937, **21**, 169.
79 W. A. Waters, *The Chemistry of Free Radicals*, 2nd edition, Oxford University Press, Oxford and London, 1948, p. 171.
80 J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, 1951, **49**, 273.
81 N. Kornblum, R. E. Michel and R. C. Kerber, *J. Am. Chem. Soc.*, 1966, **88**, 5662.
82 G. A. Russell and W. C. Danen, *J. Am. Chem. Soc.*, 1966, **88**, 5663.
83 J. Kook Kim and J. F. Bunnett, *J. Am. Chem. Soc.*, 1970, **92**, 7463.
84 J. Kook Kim and J. F. Bunnett, *J. Am. Chem. Soc.*, 1970, **92**, 7464.
85 J. F. Bunnett and X. Creary, *J. Org. Chem.*, 1974, **39**, 3173.
86 J. F. Bunnett and X. Creary, *J. Org. Chem.*, 1974, **39**, 3611.
87 J. F. Bunnett, R. G Scamehorn and R. P. Traber, *J. Org. Chem.*, 1976, **41**, 3677.
88 J. F. Bunnett and R. P. Traber, *J. Org. Chem.*, 1978, **43**, 1867.
89 J. F. Bunnett and S. J. Shafer, *J. Org. Chem.*, 1978, **43**, 1877.
90 C. Galli and J. F. Bunnett, *J. Am. Chem. Soc.*, 1981, **103**, 7140.
91 J. M. Saveant, *Acc. Chem. Res.*, 1980, **13**, 323.
92 R. A. Rossi, *Acc. Chem. Res.*, 1982, **15**, 164.
93 K. A. Bilevitch, N. N. Pubnov and O. Yu. Okhlobystin, *Tetrahedron Lett.*, 1968, **9**, 3465.
94 T. D. Tuong and M. Hida, *Chem. Lett.*, 1973, 363.
95 R. G. R. Bacon and A. Karim, *J. Chem. Soc., Perkin Trans. 1*, 1973, 272.
96 S. Arai, M. Hida and T. Yamagishi, *Bull. Chem. Soc. Jpn.*, 1978, **51**, 277.
97 S. Arai, M. Hida, T. Yamagishi and S. Ototake, *Bull. Chem. Soc. Jpn.*, 1977, **50**, 2982.
98 S. Arai, T. Yamagishi, S. Ototake and M. Hida, *Bull. Chem. Soc. Jpn.*, 1977, **50**, 547.
99 W. R. Bowman, H. Heaney and P. H. G. Smith, *Tetrahedron Lett.*, 1982, **23**, 5093.
100 C. L. Jenkins and J. K. Kochi, *J. Am. Chem. Soc.*, 1972, **94**, 856.
101 J. K. Kochi, *Organometallic Mechanisms and Catalysis*, Academic Press, New York, 1978.
102 In this type of experiment, the radical that is formed as intermediate rearranges further in a unimolecular reaction that is known to be very fast, faster than any known bimolecular reaction. Thus, not finding the rearrangement product is seen as strong evidence against the intermediacy of the radical. The hidden assumption is that the bimolecular reaction is always slower than the intramolecular rearrangement reaction.
103 R. G. R. Bacon and H. A. O. Hill, *J. Chem. Soc.*, 1964, 1097.
104 R. G. R. Bacon and H. A. O. Hill, *J. Chem. Soc.*, 1964, 1108.
105 R. G. R. Bacon and H. A. O. Hill, *J. Chem. Soc.*, 1964, 1112.
106 V. V. Litvak and U. S. M. Shein, *Z. Org. Khim.*, 1974, **10**, 2360.
107 H. Weingarten, *J. Org. Chem.*, 1964, **29**, 977.
108 R. W. Turner and E. L. Amma, *J. Am. Chem. Soc.*, 1963, **85**, 4046.
109 B. Nichols and M. C. Whiting, *J. Am. Chem. Soc.*, 1959, 551.
110 T. K. Dargel, R. H. Hertwig and W. Koch, *Mol. Phys.*, 1999, **96**, 583.
111 R. T. Stibrany, C. M. Zhang, T. J. Emge, H. J. Schugar, J. A. Potenza and S. Knapp, *Inorg. Chem.*, 2006, **45**, 9713.
112 P. Capdevielle and M. Maumy, *Tetrahedron Lett.*, 1993, **34**, 1007.
113 J.-F. Marcoux, S. Doye and S. L. Buchwald, *J. Am. Chem. Soc.*, 1997, **119**, 10539.
114 S. Zhang, D. Zhang and L. S. Liebeskind, *J. Org. Chem.*, 1997, **62**, 2312.
115 A. Ouali, J.-F. Spindler, A. Jutand and M. Taillefer, *Adv. Synth. Catal.*, 2007, **349**, 1906.
116 E. Sperotto, G. P. M. van Klink, J. G. de Vries and G. van Koten, *J. Org. Chem.*, 2008, **73**, 5625.
117 L. Rout, P. Saha, S. Jammi and T. Punniyamurthy, *Eur. J. Org. Chem.*, 2008, 640.
118 C. Savarin, J. Srogl and L. S. Liebeskind, *Org. Lett.*, 2002, **4**, 4309.
119 D. Ma, Y. Zhang, J. Yao, S. Wu and F. Tao, *J. Am. Chem. Soc.*, 1998, **120**, 12459.
120 H. Zhang, Q. Cai and D. Ma, *J. Org. Chem.*, 2005, **70**, 5164.
121 X. Guo, H. Rao, H. Fu, Y. Jiang and Y. Zhao, *Adv. Synth. Catal.*, 2006, **348**, 2197.
122 H.-C. Ma and X.-Z. Jiang, *J. Org. Chem.*, 2007, **72**, 8943.
123 Z. Lu and R. J. Twieg, *Tetrahedron Lett.*, 2005, **46**, 2997.
124 Y.-X. Xie, S.-F. Pi, J. Wang, D.-L. Yin and J.-H. Li, *J. Org. Chem.*, 2006, **71**, 8324.
125 H.-J. Cristau, P. P. Cellier, J.-F. Spindler and M. Taillefer, *Chem.–Eur. J.*, 2004, **10**, 5607.
126 H.-J. Cristau, P. P. Cellier, J.-F. Spindler and M. Taillefer, *Eur. J. Org. Chem.*, 2004, 695.
127 R. A. Altman, A. M. Hyde, X. Huang and S. L. Buchwald, *J. Am. Chem. Soc.*, 2008, **130**, 9613.
128 M. Periasamy, P. Vairaprakash and M. Dalai, *Organometallics*, 2008, **27**, 1963.
129 H. Huang, X. Yan, W. Zhu, H. Liu, H. Jiang and K. Chen, *J. Comb. Chem.*, 2008, **10**, 617.
130 K. Verma, J. Singh and R. Chaudhary, *Tetrahedron Lett.*, 2007, **48**, 7199.
131 J. P. Collman, M. Zhong, C. Zhang and S. Costanzo, *J. Org. Chem.*, 2001, **66**, 7892.
132 A. Shafir, P. A. Lichtor and S. L. Buchwald, *J. Am. Chem. Soc.*, 2007, **129**, 3490.
133 G. Evindar and R. A. Batey, *J. Org. Chem.*, 2006, **71**, 1802.
134 G. Feng, J. Wu and W.-M. Dai, *Tetrahedron Lett.*, 2007, **48**, 401.
135 E. R. Strieter, D. G. Blackmond and S. L. Buchwald, *J. Am. Chem. Soc.*, 2005, **127**, 4120.
136 E. R. Strieter, B. Bhayana and S. L. Buchwald, *J. Am. Chem. Soc.*, 2009, **131**, 78.
137 S.-L. Zhang, L. Liu, Y. Fu and Q.-X. Guo, *Organometallics*, 2007, **26**, 4546.
138 J. W. Tye, Z. Weng, A. M. Johns, C. D. Incarvito and J. F. Hartwig, *J. Am. Chem. Soc.*, 2008, **130**, 9971.
139 J. W. Tye, Z. Weng, R. Giri and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 2010, **49**, 2185.
140 E. Sperotto, G. P. M. van Klink, J. G. de Vries, G. van Koten, submitted.
141 G. O. Jones, P. Liu, K. N. Houk and S. L. Buchwald, *J. Am. Chem. Soc.*, 2010, **132**, 6205.
142 S. L. Buchwald and C. Bolm, *Angew. Chem., Int. Ed.*, 2009, **48**, 5586.
143 P.-F. Larsson, A. Correa, M. Carril, P.-O. Norrby and C. Bolm, *Angew. Chem., Int. Ed.*, 2009, **48**, 5691.
144 J. G. de Vries, *Dalton Trans.*, 2006, 421.
145 N. T. S. Phan, M. Van, Der Sluys and C. W. Jones, *Adv. Synth. Catal.*, 2006, **348**, 609.
146 L. Djakovitch, K. Köhler and J. G. de Vries, In *Nanoparticles and Catalysis*, D. Astruc, ed., Wiley-VCH, 2008, p303.
147 A. H. M. de Vries, J. M. C. A. Mulders, J. H. M. Mommers, H. J. W. Henderickx and J. G. de Vries, *Org. Lett.*, 2003, **5**, 3285.
148 X. Chen, X.-S. Hao, C. E. Goodhue and J.-Q. Yu, *J. Am. Chem. Soc.*, 2006, **128**, 6790.
149 O. Daugulis, H.-Q. Do and D. Shabashov, *Acc. Chem. Res.*, 2009, **42**, 1074.
150 F. Besselièvre and S. Piguel, *Angew. Chem., Int. Ed.*, 2009, **48**, 9553.
151 A. E. King, L. M. Huffman, A. Casitas, M. Costas, X. Ribas and S. S. Stahl, *J. Am. Chem. Soc.*, 2010, **132**, 12068.
152 R. J. Phipps and M. J. Gaunt, *Science*, 2009, **323**, 1593.