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COPPER ASSISTED NUCLEOPHILIC SUBSTITUTION OF ARYL HALOGEN

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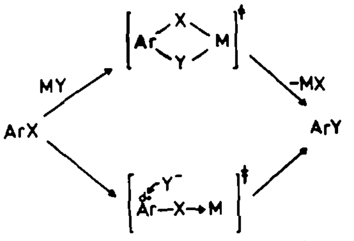
CONTENTS

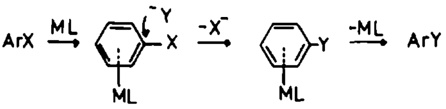
INTRODUCTION

The halogen atom in aryl halides is relatively inert to nucleophilic substitution unless it is activated by the presence of electron withdrawing groups.[1] Metals and metal complexes may participate in these reactions in a variety of ways as illustrated by the following examples.

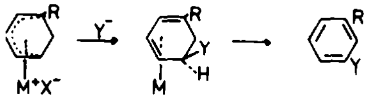
(i) The metal may form a σ-complex with the lone pairs of electrons of the halogen atom, this leads to polarisation of the carbon to halogen bond and subsequent attack by nucleophile may occur intermolecularly or intramolecularly (Scheme 1).



Scheme 1.



Scheme 2.



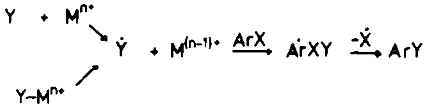
Scheme 3.

$$
\begin{aligned}
&M^{n+} + ArX \longrightarrow M^{(n+1)+} + ArX^{\overline{\cdot}}\\
&ArX^{\overline{\cdot}} \longrightarrow Ar^{\cdot} + X^{-}\\
&Ar^{\cdot} + Y^{-} \longrightarrow ArY^{\overline{\cdot}}\\
&ArY^{\overline{\cdot}} + ArX \longrightarrow ArY + ArX^{\overline{\cdot}}_{\text{etc}}
\end{aligned}
$$

Scheme 4.

$$
\begin{aligned}
&M^{n+} + ArX \longrightarrow M^{(n-1)+} + ArX^{\dot{+}}\\
&ArX^{\dot{+}} + Y^{-} \longrightarrow \dot{A}rXY\\
&\dot{A}rXY \longrightarrow ArY^{\dot{+}} + X^{-}\\
&ArY^{\dot{+}} + ArX \longrightarrow ArY + ArX^{\dot{+}}_{\text{etc}}
\end{aligned}
$$

Scheme 5.



Scheme 6.

(ii) The metal may form a π-complex in which the metal is equivalent to a strong electron withdrawing group in the aryl ring (Scheme 2).

Reactions of this type are particularly favoured with cationic π-complexes.[2] A synthetically equivalent result may be achieved by nucleophilic addition to coordinated cyclohexadienyl cations followed by demetallation and dehydrogenation of the resulting diene[3] (Scheme 3).

(iii) The metal may function as a one electron donor as in the $S_{RN}1$ reaction[4] (Scheme 4).

(iv) The metal may function as an electron acceptor as in the $S_{ON}2$ reaction[5] (Scheme 5), or as in the S_HAr reaction[6] (Scheme 6) *ipso*-Substitution in the S_HAr reaction is most common with nucleophilic radicals.

(v) The metal may undergo oxidative addition of the aryl halide, followed by reductive elimination of exchanged product.[7] (Scheme 7).

The mechanism of oxidative addition may involve either successive one electron transfers or electron pair processes.[7]

The *ipso*-substitution of aryl halide promoted by copper compounds was first reported by Ullmann in 1901,[9] and has since been used on a widespread basis. Although many of the reactions outlined in Schemes 1 to 7 occur under much milder conditions than with copper compounds there may be limitations to their utilisation in large scale synthesis. For example, reactions based on π-complexes invariably involve toxic co-ligands such as carbon monoxide or phosphines which are

$$L_nM^nY \xrightarrow{ArX} (X)(Ar)M^{n+2}(Y)L_{n-2} \xrightarrow{2L} ArY + L_nM^nX$$

Scheme 7.

Table 1. Groups replacing aryl halogen assisted by copper

Group	References	Group	References
$-NRR'$		$-SR$	
R=R′=H	90- 88	R=aryl	40-47
R=H, R′=alkyl	19-22,28-31	R=alkyl	64,67,73-76
R=H, R′=aryl	16-18, 23	R=acyl	77
R=R′=aryl	24,25	R=CN	66,67
R=H, R′=acyl	32-38		
R=H, R′=SO_2R	39	$-SO_2R$	60-62
$-N_3$	89	$-P(O)(OR)_2$	90-98
$-NO_2$	60,61	$-\overset{+}{P}R_3$	90,93,99
$-OR$		$-CRR^1R^2$	
R=aryl	40-47	R=H, $R^1=R^2=CO_2Et$	100,107,110-114
R=alkyl	48-51	R=H, $R^1=R^2=COR$	100-104,107,110-112
R=acyl	57-59	R=H, R=CN, R=CO_2Et	112,115
$-$Halide	52,66,80-88	$-C{\equiv}R$	
	156,158.	R=N	66,116-122
$-SeCN$	79	R=CR	124-130

themselves nucleophilic and may promote side reactions. $S_{RN}1$ reactions require solvents with a low affinity for the aryl radical and of low acidity; liquid ammonia is commonly used, or the reaction may require photostimulation. For these and other reasons copper promoted *ipso*-nucleophilic reactions seem to be favoured for reactions carried out on an industrial scale.

In this review emphasis will be placed on work published since earlier reviews of this topic.[8]

Scope of copper assisted nucleophilic displacement of aryl halogen

The range of nucleophiles which have been used is shown in Table 1. Reductive dehalogenation and biaryl coupling in addition to the nucleophilic substitution may be observed in varying amounts. The ease of halogen displacement from the aromatic ring is generally $I > Br > Cl \gg F$, this is the opposite trend to that observed in uncatalysed S_NAr reactions.[1] Generally, the reactions are influenced to a slight extent only by the presence of substituents meta or para to the halogen, although the presence of a potential chelating group (e.g. — NO_2; — COR; R=H, Alkyl, OH, OAlkyl; CN) in the ortho position has a marked activating effect. Compounds of the last type will be referred to as activated aryl halides.

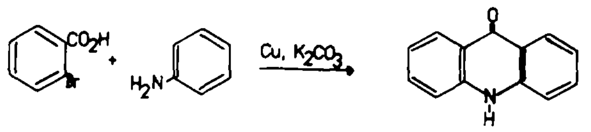
Reaction with nitrogen nucleophiles

With ammonia. Ammonation of aryl halides catalysed by copper is well known and is carried out extensively on an industrial scale.[9] For unsubstituted aryl halides the reaction is generally carried out at temperatures in excess of 150° in aqueous solution. A wide variety of copper catalysts have been used, with copper in the 0, + 1 or + 2 oxidation states. Activated aryl halides can be ammonated at much lower temperatures, for example the industrially important ammonation of 1-bromoanthraquinones occurs in high yield at 80°.[10] Reductive dehalogenation and phenol formation often compete with ammonation. A kinetic study of the ammonation of chlorobenzene shows that the activation energy for the copper(II) catalysed reaction is twice that for the copper(I) catalysed reaction.[12]

Shein *et al.*[13] found that the ammonation, of o-chloronitrobenzene promoted by copper(II) chelate complexes is first order in both complex and aryl halide but zero order in ammonia. In a subsequent publication,[14] these authors showed that the ammonation of o-chloronitrobenzene in aqueous dioxane using copper(II) acetate, copper(II) bipyridyl or copper(II) oxinate gave 100% yields of o-nitroaniline, whereas when copper(I) chloride, copper(II) glycinate or copper(II) acetylacetonate are used nitrobenzene is also produced in equimolar amounts to the copper complex used. ESR studies showed that this reductive dehalogenation is associated with the rapid reduction of copper(II) to copper(I) by the ligand in these latter complexes, followed by single electron transfer from copper(I) to give the o-chloronitrobenzene radical anion. A change of solvent to ethanol or ethylene glycol also led to some reductive dehalogenation in the systems in which it was absent in aqueous dioxan.

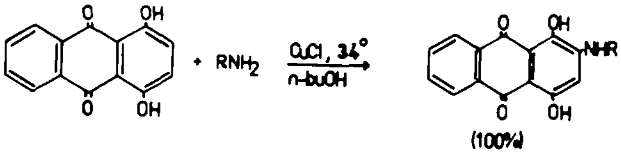
A new procedure for the ammonation of aryl halides with hydrolytically unstable substituents utilises copper(II) chloride and a large excess of potassium fluoride in non-aqueous solvents such as benzonitrile, acetonitrile and alcohols.[15]

With amines. The Ullmann condensation of amines with aryl halides is similar in many respects to the ammonation. The reaction occurs under mild conditions with activated aryl halides and the reaction of o-halobenzoic acids with phenylamines is a key step in the synthesis of acridines (eqn 1).[16]



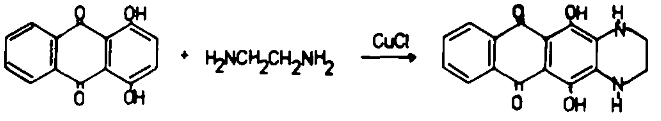
1

The reaction is also used extensively in the synthesis of o-arylaminodiarylazo dyes,[17] and 1-aminoanthraquinones.[18] The direct displacement of aromatic hydrogen by alkylamines promoted by copper(I) chloride has been reported for α-substituted anthraquinones (eqn 2).[19–21]



2

With primary 1,2-diamines ring closure products are obtained (eqn 3).[22]



3

The Ullmann condensation of aryl halides with amines is traditionally carried by heating with copper powder in the presence of bases such as sodium carbonate or hydroxide.[23] A variation involves heating the aryl halide and amine with copper powder in the absence of solvent, in this way triphenylamine was obtained in 86% yield.[24] The use of copper(I) oxide and copper(I) bromide in the condensation of diphenylamine and o-bromonitrobenzene in DMA is reported to be less effective than the traditional method.[25] The condensation of 1-bromoanthraquinones with aniline in aqueous solution is catalysed by copper(II) salts, however, kinetic and ESR studies indicate that the effective catalyst is a copper(I) species.[18,26,27] Further evidence in support of this comes from the marked accelerating effect produced by reducing agents such as Sn^{2+}, Fe^{2+} and Ti^{3+} and the inhibition caused by molecular oxygen. This condensation is also favoured by an increase in the hydroxide ion concentration. The hydroxide ion is thought to deprotonate the amine and thereby facilitate the reduction of copper(II) (eqn 4).

$$L_nCu^{II}NH_2Ph \overset{OH^-}{\rightleftharpoons} L_nCu^{II}\bar{N}HPh \rightleftharpoons L_nCu^{I}\dot{N}HPh \qquad 4$$

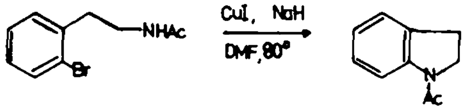
During the condensation of 1-bromoanthraquinone with 2-aminoethanol in aprotic solvents an induction period is observed when copper(I) bromide or iodide are used as catalysts. This induction period was found to be associated with the formation of a copper(II) species, since the induction period vanishes when copper(II) bromide is added.[28,29] The ESR spectrum of the 1-bromoanthraquinone, aminoethanol, copper(I) bromide system showed the presence of both a copper(II) species and the 1-bromoanthraquinone radical anion.[30,31] Although the copper(II) species alone was found to have little catalytic activity it led to an increase in the activity of copper(I).

With imides and amides. Copper(I) compounds promote the reaction between aryl halides and potassium phthalimide to give N-arylphthalimides, subsequent hydrolysis of the product leads to primary aromatic amines. The two step process represents an extension of the Gabriel reaction to aryl halides. Copper in the 0, +1 and +2 oxidation states is effective, however, the best yields were obtained with copper(I) iodide in DMA at 165°.[32] A high copper(I) iodide to phthalimide ratio increases the reaction rate, electron attracting substituents in the para position of the aryl halide have a small accelerating effect and steric inhibition is observed with 2-substituted aryl halides and polycyclic halides.[32] Subsequently,[33] this work was extended to include the reactions of succinimide, maleimide, dibenzamide, benzenesulphonamide and benzenesulphanilide with bromobenzene, although yields were substantially lower than those with phthalimide. This type of reaction is also applicable to vinyl and aromatic heterocyclic halides.

Copper(I) oxide has also been used to promote the reaction of phthalimide with phenyl and ferrocenyl halides.[34]

Comparable yields to those obtained using copper(I) iodide and potassium salts of imides or amides are obtained when the copper complexes $R^1R^2N\ Cu(P(C_6H_5)_3)_3$ (R^1R^2N = phthalimido, succinimido, N-phenylacetamido, acrylamido, phenylamido and 2-oxo-1-pyrrolidinyl) react with aryl halides in diglyme at 170°.[35]

Condensation of amides (benzamide, acetamide, pyrroldine-2-one) with aryl halides by heating with copper powder at temperature in excess of 150° in the absence of solvent is also reported to give good yield of N-arylamides.[36] Intramolecular condensation of 2-halobenzylamides to yield indole derivatives is promoted by copper(I) iodide and sodium hydride in DMF at 80° (eqn 5).[37]



5

Condensation of activated aryl halides with primary sulphonamides in the presence of copper salts to give N-aryl sulphonamides was first reported by Ullmann.[38] The reaction has been extended to synthesis of N,N-diarylsulphonamides by the reaction of N-aryl sulphonamides with unactivated aryl bromides in the presence of copper powder and potassium carbonate at 180°.[39]

With azide. There is just one report of the synthesis of aryl azides by the reaction of aryl iodides with sodium azide and copper(I) iodide in HMPT.[89]

Reaction with oxygen nucleophiles

With phenols and phenoxide. The Ullmann phenyl ether synthesis is a well established method.[40] The classical method involves heating aryl halides with potassium phenoxide at about 200° in the presence of a small quanitity of copper powder and air. Yields of 70–80% are often obtained, although with methyl and methoxy substituted halides or phenols yields fall to about 50%, and with polyfunctional reagents low or negligible yields are often obtained.[41,42] In a study of the condensation of 1-naphthyl halides with phenol in collidine at 170° copper(I) oxide is reported to be a superior reagent to copper powder, copper(I) halides or copper(II) oxide.[41] However, when sodium phenoxide is used instead of phenol then DMA is a better solvent than quinoline.[41] Methyl, methoxy or chloro substituents in the phenol or halide have little effect on the etherification, although a small amount of reductive dehalogenation also occurs. However, when carboxyl or nitro substituents are present ether formation is suppressed and reductive dehalogenation becomes the major process. A Further problem with carboxyl functions under these conditions is decarboxylation. These condensations are also subject to marked solvent effects. For example, reactions carried out in primary aliphatic amine led to a marked increase in the rate of etherification, whereas those carried out in secondary amine or amide solvents gave very low yields of ether.[41] The condensation of disodium resorcinate with bromobenzene in the presence of copper(I) chloride to give 1,3-diphenoxybenzene gave a 74% yield for the reaction in pyridine, whereas 20% yields were obtained for the reactions in collidine, DMF, DMA, HMPT and DMSO under comparable conditions, and in the presence of 2% water the yield of ether from the reaction in pyridine fell to 4%.[42] Other points arising from the above work are the observations that excess base completely inhibits the etherification and the presence of molecular oxygen leads to tar formation at the expense of product. Improved yields of phenyl ethers are reported to be obtained when copper(II) basic carbonate or copper(II) carboxylates are used as catalysts, thus a 69% yield of

3-phenoxytoluene is obtained from chlorobenzene, potassium m-cresolate and copper(II) carbonate compared with only 25% using copper(II) halides.[43]

It is generally assumed that a copper(I) phenoxide complex is formed in these reactions and copper(I) phenoxide has been shown to react with bromobenzene in diglyme to give diphenyl ether. The addition of three mole equivalents of pyridine gave an increased yield of ether, whereas the same quantity of triphenyl phosphine drastically reduced the yield.[44,45]

A kinetic study of the reaction of potassium phenolate with substituted aryl bromides in 1:1 pyridine–phenol solvent in the presence of copper(I) bromide revealed both a copper catalysed route and an uncatalysed route to ether formation.[46] In most cases studied the catalysed process occurred at a very much higher rate than for the uncatalysed process. The Hammett ρ constant of $+6.6$ for the uncatalysed process is typical for reactions which proceed via the S_NAr mechanism, however, the ρ constant for the copper catalysed process is only $+0.61$.

When copper(II) chloride, copper(II) acetate and copper(I) halides were used to promote the reaction of potassium phenate with bromobenzene in diglyme it was found that for equal weights of copper the rates of reaction are identical. These results suggest a common intermediate which was suggested to be a copper(I) species since the reactions are also much slower in the presence of oxygen.[47]

With alcohols and alkoxides. High yields (80–100%) of alkyl aryl ethers are obtained from the reaction of aryl halides with the alkoxides of primary aliphatic alcohols in the presence of copper(I) iodide in 2,4,6-collidine at 100–120°.[48] This contrasts with the behaviour in the heterogeneous system using copper(I) oxide where the major reaction is reductive dehalogenation.[49] Heterocyclic base solvents were found to be better than polar solvents such as DMA and the optimum ratio of aryl halide–alkoxide–copper(I) iodide was found to be 1:3:0.5. Since the ethers yield phenols on hydrolysis this method is proposed as a useful alternative to traditional phenol syntheses.[48] In a study of the reaction of alkoxide with aryl halides of the type $C_6H_{5-n}X_nHal$ (Hal = I,Br; $X = OCH_3$) in the presence of copper(I) iodide three categories of aryl halide could be recognised.[50] The first in which there are no ortho substituents give high yields of ethers, although the yields tend to fall with an increase in the number of methoxy groups. In the second category of aryl halide there is one ortho methoxy group and with these halides appreciable reductive dehalogenation accompanies ether formation. The third category of aryl halides contain two ortho methoxy groups and in these cases reductive dehalogenation is the major reaction. The extent of reductive dehalogenation was found to be greater with aryl iodides than with aryl bromides. The reaction of copper(I) alkoxides, formed by the reaction of methylcopper(I) with alcohol, with aryl halides to give ethers occurs at room temperature but is markedly solvent dependent. Thus copper(I) n-butoxide reacts with iodobenzene at 25° to give a 64% yield of n-butyl phenyl ether in pyridine but only a 1% yield is obtained in diglyme.[51]

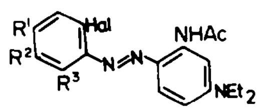
With carboxylate. The reaction of aryl halides with carboxylate ions or carboxylic acids in the presence of copper salts often leads to reductive dehalogenation.[52] A further complication may arise from the decarboxylation of the copper(I) carboxylates to give organocopper compounds; in the case of the decarboxylation of copper(I) pentafluorobenzoate in quinoline the intermediate pentafluorophenyl copper has been isolated.[53,54] These organocopper compounds generally undergo cross coupling with aryl halides to give an unsymmetrical biphenyls, oxidative coupling to give symmetrical biphenyls or hydrolysis to arenes. The decarboxylation/cross coupling procedure has recently been utilised as a simple route for the introduction of the strong electron withdrawing — CF_3 group into aromatic compounds[55] (eqn 6).

$$\mathrm{ArHal} + \mathrm{CF_3CO_2Na} \xrightarrow[\text{N-me.pyrrolidone}]{\text{CuI, }160^\circ} \mathrm{ArCF_3}\ (47\text{–}88\%) \qquad 6$$

Decarboxylation of aromatic acids in the presence of copper(I) oxide and ammonia gives good yields of aromatic amines.[56] The decarboxylation is markedly solvent dependent, the rate decreasing in the sequence quinoline ≫ tri-n-butylamine > nitrobenzene > tetraglyme.[53]

However, the substitution of aryl or vinyl halogen by benzoate occurs in high yields when the corresponding halides are reacted with copper(I) benzoate in diglyme, pyridine or xylene at 140–160° under rigorously anhydrous conditions.[57] Attempts to prepare aryl acetates from aryl halides and copper(I) acetate under similar conditions were unsuccessful.[58]

Recently the nucleophilic displacement of halogen by acetate in o-halodiarylazo compounds of type I, promoted by copper(II) acetate in DMSO or DMF has been reported to occur at room temperature.[59]



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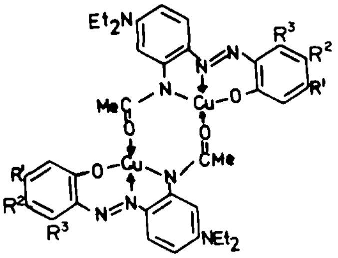


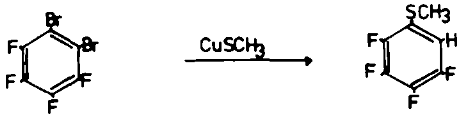
II

In o-halodiarylazo compounds with two halogen atoms only the ortho halogen is displaced. The o-acetoxydiarylazo compounds undergo facile hydrolysis to give an annelated copper(II) o-hydroxydiarylazo complex **II**, which can be demetallated by treatment with 2M hydrochloric acid to yield o-hydroxydiarylazo compounds. Only those o-halodiarylazo compounds with a potential chelating group in the 2-position in the non-halogen containing ring undergo this reaction. When the reaction is carried out in N-heterocyclic solvents or ethanol higher temperatures are required and the yields are much lower than those in DMSO or DMF.

Reaction with sulphur nucleophiles

With arene thiolate. Unactivated aryl chlorides or bromides react with copper(I) phenylthiolate in quinoline at 200° to give good yields of diaryl sulphides, the reaction is also applicable to heterocyclic and vinyl halides.[63,64] High yields of diaryl sulphides are also obtained by the reaction of aryl iodides with alkalimetal aryl thiolates and copper(I) iodide in HMPT at 70–80°.[65] 1-Naphthyl bromide reacts with copper(I) phenylthiolate in pyridine at 115° to give a 26% yield of phenyl 1-naphthyl sulphide, whereas the reaction with sodium phenyl thiolate and copper(I) oxide in DMF at 153° gives a 99% yield of the same product.[66,67] Copper(I) arene thiolates have been used extensively for the displacement of bromo in bromoperfluoroaromatics.[68–70] Copper(I) arene selenolates react with unactivated aryl iodides in HMPT at 120° to give good yields (66–94%) of diaryl selenides.[71,72]

With alkyl thiolates. Unactivated aryl bromides or iodides and activated aryl chlorides react with copper(I) alkyl thiolates in quinoline at 200° to give good yields of alkyl aryl sulphides.[64] 1-Naphthyl bromide reacts with sodium ethyl thiolate and copper(I) oxide in DMF at 150° to give a 95% yield of ethyl naphthyl sulphide.[67] Copper(I) trifluoromethyl thiolate is a useful reagent for the introduction of a CF_3S group into a wide range of aromatic and heteroaromatic compounds.[73] Oxidation of the CF_3S group to the corresponding sulphone represents a convenient means of introducing the powerful electron withdrawing — SO_2CF_3 group into the aromatic ring. High yields of aryl trifluoromethyl sulphides are also obtained by the reaction aryl bromides with mercury(II) trifluoromethyl thiolate and copper dust in DMF at 120°.[74] Copper(I) methyl thiolate reacts with 1,3- or 1,4-bromotetrafluorobenzene to give the corresponding bis(methylthio) tetrafluorobenzene, whereas 1,2-dibromotetrafluorobenzene gives 2-methylthio-3,4,5-tetrafluorobenzene (eqn 9) and bromopentafluorobenzene reacts with sodium methyl thiolate in the absence of copper to give



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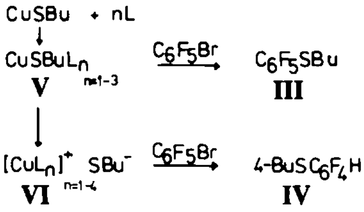
fluorine displacement.[75] Copper(I) n-butylthiolate reacts with bromopentafluorobenzene according to eqn (10).[76]

$$C_6F_5Br + CuSBu \longrightarrow \underset{\textbf{III}}{C_6F_5SBu} + \underset{\textbf{IV}}{4\text{-}BuSC_6F_4H} \qquad 10$$



Scheme 8.

The ratio of products **III** to **IV** is solvent dependent. Thus in DMF **III** is the sole product, whereas in DMF containing four equivalents of thiourea **IV** is the sole product. Solvents such as N-heterocyclic bases which are good ligands for copper(I) also lead to substantial debromination. These results were interpreted in terms of the reactions in Scheme 8.

In the presence of weak ligands such as DMF the butylthiolate ion remains coordinated to copper and reaction with aryl bromide leads to bromine displacement. However, in the presence of strong ligands, such as thiourea or pyridine, ionic complexes of type **VI** are formed. Under these conditions the free butylthiolate ions attack the fluorine in the para position to bromine, which represents the normal course of the reaction of pentafluorobromobenzene with alkali metal thiolates, followed by reductive debromination promoted by copper.

With other sulphur nucleophiles. Good yields (71–91%) of S-aryl thiobenzoates are obtained from the reaction of unactivated aryl iodides with copper(I) thiobenzoate in HMPT at 100–110°.[77] Subsequent hydrolysis of the S-aryl thiobenzoates yields aryl thiols, therefore these reactions represent a simple two step route to these products from aryl iodides. Low yields of 1-naphthyl thiocyanide are obtained in the reaction of 1-naphthyl bromide with copper(I) thiocyanate in pyridine at 115°.[66] Although it is not a nucleophilic substitution it is of interest that copper(II) thiocyanate is a useful reagent for thiocyanation of aromatic compounds.[78]

Polymethylaryl iodides are converted into the corresponding selenocyanide by their reaction with potassium selenocyanide and copper(I) iodide in HMPT, however, the corresponding reaction with tellurocyanide leads to aryl nitriles and with the thiocyanide to diaryl sulphides.[79] Copper(I) and copper(II) sulphinates promote the displacement of halogen in 1-haloazulenes by sulphonyl group.[60,61] The reaction with copper(II) compounds occurs more rapidly than with the corresponding copper(I) compound, and the copper(II) promoted reaction is accelerated by the presence of a copper(II) compound with poor coordinating groups such as copper(II) tetrafluoroborate. The reaction using copper(II) phenyl sulphinate is also applicable to other aryl halides such as 1-iodonaphthalene and 4-bromo-N,N-dimethylaniline.[62] These reactions have all the hallmarks of electrophilic substitutions; the electrophile being considered to be formed by oxidation of the phenylsulphinate ion by copper(II) and the copper(I) formed in this oxidation is subsequently reoxidised by single electron transfer to aryl halide eqns (7) and (8).

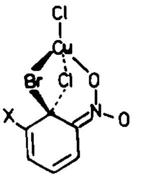
$$CuX_2 + CuX^+ \rightleftharpoons X^+ + 2CuX \qquad 7$$

$$ArHal + X^+ + 2CuX \longrightarrow ArX + CuHal^+ + CuX_2 \qquad 8$$

It should be noted, however, that free phenyl sulphonyl cations are not generated in this system, since $PhSO_2^+$ formed in the exchange reaction of $PhSO_2Cl$ and $AgBF_4$ was found to be inactive in the ipso-halosubstitution.[62]

Reactions with halide

An early study[66] of halogen exchange in 1-halogenonaphthalene promoted by copper(I) compounds established that the ease of displacement of halogen from the aryl halide is I > Br > Cl and that the ease of entry to halogen from the copper compound is Cl > Br > I. The reactions exhibit second order kinetics and the second order rate constants vary by a factor of 200 for a range of solvents; rates in polar solvents such as DMSO, DMF, HMPT being greater than those in N-heterocyclic base solvents. The addition of potential ligands for the copper(I) atom, for example, pyridine, 2,2′-dipyridyl or alkali metal halides, causes inhibition of the reaction in DMSO.[66] Pyridine when added in a 1:1 mole ratio to copper, however, is found to enhance the rate of chlorine-bromine exchange in bromobenzene. The presence of electron withdrawing groups in the 3 or 4 position in the pyridine ring increases the rate, whereas, substituents in the 2 position retard the rate irrespective of their electronic properties.[81] Liedholm,[82-85] studied the kinetics of halogen exchange in a series of substituted-2-bromonitrobenzenes promoted by copper(I) chloride in aqueous hydrochloric acid. The active copper species in this system is considered to be $CuCl_2^-$. The second order rate constants show little variation when the third substituent is in the para position to the halogen, however, when it is in the ortho position there is significant rate enhancement. The rate increases with increasing Van der Waals radius of the ortho substituent and the reactions have large negative entropies of activation. This is attributed to the release of steric strain in going from the reactants to the transition state, which is considered to be a tetrahedral complex of type **VII**.



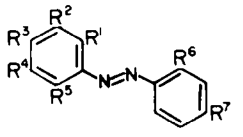
VII

Copper(I) promoted iodine exchange has been used in the synthesis of radio iodine labelled aryl iodides, these reactions occur under mild conditions (70–90°) in aprotic solvents.[86] Bromo–chloro exchange promoted by copper(I) chloride is proposed as a convenient route to 3-chloroanthraquinone, since direct chlorination gives only low yields compared with bromination. For similar reasons copper(I) promoted exchange of iodo by chloro or bromo has been proposed as a convenient route to chloro or bromoferrocene.[88]

Reaction with phosphorus nucleophiles

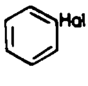
With phosphite esters. Unactivated aryl iodides and bromides react with trialkyl phosphites in the presence of copper bronze at 150° to give low to moderate yields of dialkyl aryl phosphonates.[90,91] Higher yields of dialkyl aryl phosphonates are obtained from the reaction of aryl iodides with sodium dialkyl phosphite and copper(I) iodide in HMPT at 150°.[92,93]

o-Bromodiarylazocompounds, **VIII** R^1=Br and certain activated aryl halides, such as methyl 2-iodobenzoate, 2-iodonitrobenzene and 1-bromoanthraquinone, react with triethylphosphite and copper(II) acetate in anhydrous ethanol under reflux to give good yields of diethyl arylphosphonates, **VIII** (R^1=P(O)(OEt)$_2$).[94] This phosphonation is subject to steric effects, thus compounds **VIII** in which R^5 is a substituent other than hydrogen react more readily irrespective of their polar nature. Bromo in positions other than ortho to the azo group are inert to phosphonation under these conditions. The reaction is also facilitated by the presence of a potential chelating group in the 2′ position (e.g. **VIII** R^6=NHAc).

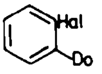


VIII

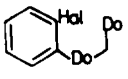
On the basis of these results Hall and Price[94] classified the halides into three types. Type **XI**, in which there are two potential ligands for copper, are more reactive than type **X** in which there is only one donor group, and type **IX**, which have no donor substituent, are inert to phosphonation under these conditions. In 10% aqueous ethanol phosphonation is accompanied by reductive dehalogation with type **XI** halides but not with type **X** halides. Copper(II) acetate is readily reduced to copper(I) acetate and acetic acid by triethylphosphite in aqueous ethanol and the type **XI** halides were shown to readily undergo reductive dehalogenation and Ullmann biaryl coupling in the presence of acetic acid, or better trifluoroacetic acid, and copper(I) acetate in ethanol.[94] The phosphonation was found to proceed readily in DMSO, DMF and N-methyl pyrrolidone and more slowly in THF and chlorobenzene.



IX



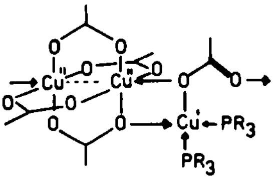
X



XI

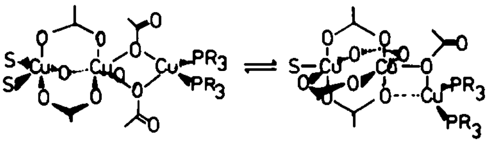
Diarylazophosphonates (VIII $R^1 = -P(O)(OR)_2$) can also be prepared in high yield by the reaction of o-bromodiarylazo compounds with diethylphosphite in the presence of copper(I) iodide and sodium acetate in dry ethanol.[95] With diphenyl phosphite the phenyl groups are replaced by the alkyl group of the alcohol used as solvent, thus providing a general method for the preparation of a range of dialkylarylphosphonates.

Anhydrous copper(II) acetate reacts with triethyl phosphite under anaerobic conditions in dry ethanol under reflux to form a mixed valence copper complex, with the crystal structure **XII**.[96]



XII

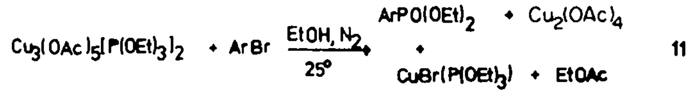
In alcohol solution the polymeric chain is broken to give a fluxional monomeric species **XIII** and **XIV** (Scheme 9).



XIII S = solvent, R = OEt **XIV**

Scheme 9.

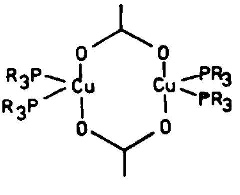
This mixed valence complex promotes the phosphonation of type **X** and **XI** bromodiarylazo compounds in dry ethanol at room temperature (eqn 11).[97]



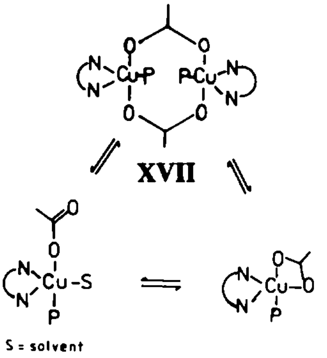
$$Cu_3(OAc)_5[P(OEt)_3]_2 + ArBr \xrightarrow[25^\circ]{EtOH,\ N_2} \begin{matrix} ArPO(OEt)_2 + Cu_2(OAc)_4 \\ + \\ CuBr(P(OEt)_3) + EtOAc \end{matrix} \qquad 11$$

The phosphonation is accompanied by small amounts of reductive dehalogenation (ca 5%) and biaryl coupling (ca 6%). When the reaction was carried out in the dark biaryl coupling was completely inhibited and reductive dehalogenation substantially reduced, the addition of radical scavengers (dpph) had a similar effect. The phosphonation in ethanol follows second order kinetics being first order in both aryl halide and **XII**, when the reaction is carried out in THF the phosphonation no longer follows second order kinetics and the yield of reduction product and biaryl increases.

The trimeric complex **XII** is split into copper(II) acetate and the dimeric triethylphosphite copper(I) acetate complex **XVI** by monodentate ligands and solvents such as THF, dioxan, diethyl ether, dichloromethane and chloroform.



XVI



Scheme 10.

The complex **XVI** also promotes the phosphonation of type **X** and **XI** o-bromodiarylazo compounds in ethanol at room temperature but more slowly than **XII** and the yield of biaryl is significantly increased. The dimeric complex **XVI** reacts with bidentate nitrogen and phosphine ligands to form complexes of stoicheiometry [Cu(OAc) ($P(OEt)_3L$], **XVII**, which are dimeric in the solid state but exist as fluxional monomers in solution, (Scheme 10). The complex **XVII** (L = bipyridine) also promotes the phosphonation of type **X** and **XI** bromobiarylazo compounds but more slowly than either **XII** or **XVI** and the yield of biaryl is substantially increased (23% for **VIII** $R^1 = Br$, $R^3 = R^5 = NO_2$, $R^6 = NHAc$, $R^7 = NMe_2$).

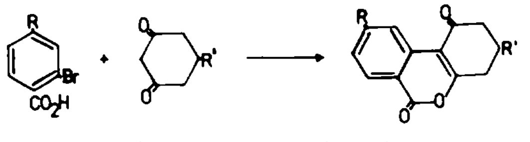
The rate of phosphonation increased markedly when the last reaction was carried out in the dark and the yield of biaryl fell to 1%. However, during the early stages of the dark reaction the yield of biaryl was as high as 53% and then decreased. The biaryl was shown to be unaffected by the reaction conditions and it was considered that the yield of biaryl is proportional to the amount of aryl radicals in solution and that the coupling of these radicals occurred when samples were removed for analysis in the light.[97]

Vinyl halides are converted in high yields and with retention of stereochemistry into dialkyl vinylphosphonates by reaction with trialkylphosphitecopper(I) halide complexes.[98]

With tertiary phosphines. Unactivated aryl halides react with tertiary phosphines in the presence of copper to give phosphonium salts.[90] o-Bromodiarylazo compounds react with tributyl or triphenylphosphine and copper(II) acetate to give the corresponding phosphonium bromide.[99]

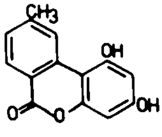
Reaction with carbon nucleophiles

With active methylene carbanions. As long ago as 1929 Hurtley reported that the reaction of 2-bromobenzoic acid with the anions of diethylmalonate, ethyl acetoacetate and benzoylacetone in anhydrous ethanol is catalysed by copper powder or copper(II) acetate, the products being C-2-carboxyphenyl derivatives or simple transformation products of them.[100] Since then there have been many reports of the utilisation of the Hurtley reaction. Adams[101-104] used 1,3-cyclohexanedione in the synthesis of cannabinoids (eqn 12).

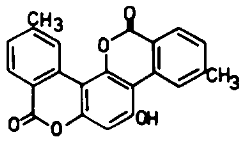


12

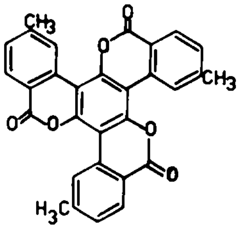
1,3-Dihydroxybenzenes may also be coupled with 2-bromobenzoic acid to give coumarins.[105-108] Rigby[105] isolated compounds **XVIII**, **XIX** and **XX** from the reaction of 2-bromo-4-methylbenzoic acid with phloroglucinol.



XVIII,

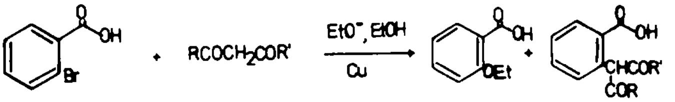


XIX,



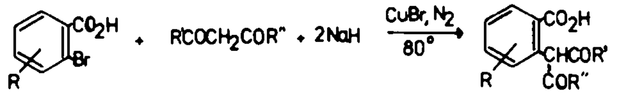
XX

It was established[109] that only potentially tautomeric phenols are active in these reactions. Cirigottis *et al.*[107] after a detailed study of the reactions of o-bromobenzoic acid with benzoylacetone concluded that: (i) copper(I) is the effective catalyst (ii) dry ethanol is the best solvent for the reaction; no reaction was observed in DMSO or pyridine and (iii) replacement of the carboxyl group by other functionalities prevents the reaction. Broadly similar results were obtained by Bacon and Murray,[110] however, these workers suggested that a copper(II) species is the effective catalyst. Ames and Dodds,[111] extended the Hurtley reaction to o-halonicotinic acids, which are found to react with simple β-dicarbonyl compounds but not C-alkylated derivatives. The low to moderate yields reported for the Hurtley reaction led Buggink and McKillop to investigate the reaction conditions, they found that a major competing reaction is halosubstitution by the conjugate base of the solvent (eqn 13).[112]



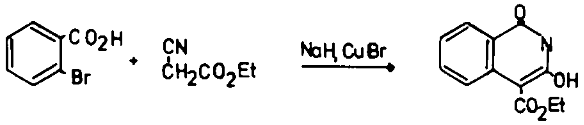
13

Investigation of other base-solvent systems led to the development of an improved method based on eqn (14).



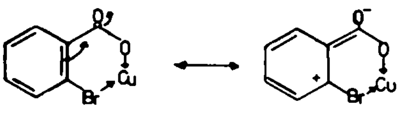
14

For small scale reactions the β-dicarbonyl compound was used in excess but for large scale operations a diluent such as toluene is recommended. This method gives high yields for X = Cl,Br except where the R group is in the 3-position. Improved yields were also obtained for the reaction of 2-bromonicotinic acid (77% vs 25% by Hurtley method) and 8-bromo-1-naphthoic acid (84% vs 0%) with diethylmalonate by this method.[112] It was concluded that a β-carbonyl group is an important feature of the carbanion since attempts to utilise the carbanions of cyclopentadiene, nitromethane and dimethylsulphoxide were unsuccessful, although ethyl cyanoacetate gave a moderate yield of isoquinoline derivative (eqn 15).



15

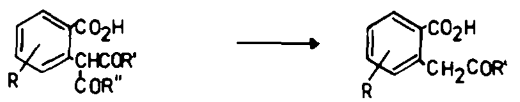
Attempts to utilise other o-haloaryl compounds, 2-BrC$_6$H$_4$X (X = CO$_2$Et, CONH$_2$, CH$_2$OH, NO$_2$, CHO, CN, SO$_3$H, CONHOH) is this reaction were unsuccessful and low yields were obtained with 2-bromophenylacetic acid.[112] From these results it was concluded that a major factor in the Hurtley reaction is the formation of a copper chelate **XXI**. Mesomerism to **XXII**, Scheme 11 is considered to be of lesser importance because the reaction proceeds very readily with 8-bromo-naphthoic acid in which this type of mesomerism is impossible.



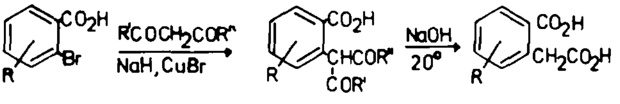
XXI **XXII**

Scheme 11.

In the classical Hurtley reaction complications may arise from a retro-Claisen reaction of the expected product (eqn 16).[110,112]


16

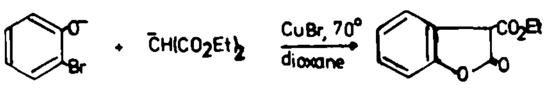
This reaction is promoted by ethoxide or hydroxide ion and does not occur with the NaH method, this has led to the development of an efficient two step synthesis of homophthalic acids (eqn 17).[112]


17

Recently the coupling of unactivated aryl bromides and iodides with diethylmalonate has been reported (eqn 18).[113]

$$\mathrm{ArX} + \mathrm{NaCH(CO_2Et)_2} \xrightarrow[\text{dioxane}]{\text{CuY},100^\circ} \underset{\textbf{XXIII}}{\mathrm{ArCH(CO_2Et)_2}} + \underset{\textbf{XXIV}}{\mathrm{ArCH_2CO_2Et}} \qquad 18$$

The reaction proceeds smoothly in HMPT, diglyme and dioxan but fails in pyridine, although the reaction is heterogeneous in dioxane yields are not significantly different from those in HMPT in which it is homogeneous. The ratio of PhI:malonate:CuI is important, thus after 5 hours in dioxane at 101° a ratio of 1:2:2 gave a 97% yield, 1:1.2:1.2 gave a 66% yield and 1:2:0.5 gave only a 38% yield. The presence of added ligands also led to lower yields. For example, NaBr(61% yield), Me_2S(52%), Ph_3P(6%) and NaI(trace) when added in a ratio of one mole per mole of copper. The activity of the copper salt was found to be CuBr > CuI > $Cu(CH_3CN)_4BF_4$ > CuCl.[13] This method has been applied to the synthesis of heterocyclic compounds e.g. eqn (19).[114]

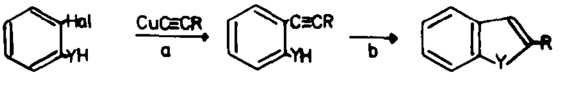

19

Unactivated aryl iodides are also reported to react with ethyl cyanoacetate and copper(I) iodide in HMPT at 90–95° to give 50–90% yield of ethyl arylcyanoacetates.[115]

With cyanide. The conversion of aryl halides into nitriles by reaction with copper(I) cyanide is a well established method.[116] The reaction, known as the Rosenmund–Von Braun reaction, is usually carried out by heating the aryl halide with copper(I) cyanide at 100–200° traditionally in solvents such as pyridine or quinoline, however, improved yields are obtained in polar aprotic solvents such as DMF and DMSO.[66,116,117,120] Yields of benzonitrile obtained in the reaction of bromobenzene with copper(I) cyanide in nitrobenzene at 180° were increased by the addition of pyridine in 1:1 mole ratio copper.[118] Anionic copper(I) cyano complexes were found to be inferior to copper(I) cyanide in the cyanation of aryl and vinyl halides in DMF, despite their having higher solubilities.[119]

2-Halobiarylazo compounds are readily converted into the 2-cyano derivatives by reaction with copper(I) cyanide,[121] or with formaldoxime, copper(I) iodide and sodium acetate in acetic anhydride.[122] In the presence of strong bases the 2-cyanodiarylazo compounds are cyclised into 3-amino indazoles.[123]

With alkynide. The reaction of aryl halides with copper(I) alkynides is known as the Castro reaction.[124] It is an important route to the synthesis of a wide range of tolane and heterocyclic derivatives. The latter are derived from aryl halides which contain a nucleophilic substituent in the 2-position (eqn 20).


20

The reaction 20a is usually carried out in pyridine or DMF at 100–120°. The cyclisation 20b is catalysed by copper(I) halides and proceeds best under heterogeneous conditions, this may be achieved by concentrating the solution or by adding excess copper(I) chloride. Oxidising agents must be avoided in reactions with copper(I) alkynes as they tend to promote oxidative coupling of the alkyne.[125] The alkynide ion bears an electronic similarity to the cyanide ion discussed above and the reactions of their copper(I) compounds with aryl halides are broadly similar.

The reaction of aryl halides with copper(I) alkynes in amine solvents is catalysed by bis(triphenylphosphine)-palladium(II) chloride, this procedure enables the reaction to occur at ambient temperature with a wide range of aryl halides,[126] and heterocyclic halides.[127,128] In non amine solvents the presence of a quaternary ammonium salt is necessary to avoid oxidative coupling of the alkyne.[129] The coupling of copper(I) alkynide and aryl halides is also catalysed by nickel complexes.[136] With ethyne disubstitution becomes the major process in the catalytic system, however, a convenient route to aryl ethynes is the two step procedure in which trimethylsilylethyne is reacted with aryl halide, followed by hydrolysis of the trimethyl silyl group with dilute alkali (eqn 21).[130]

$$\mathrm{ArHal} + \mathrm{HC{\equiv}CSiMe_3} \xrightarrow[\mathrm{NEt_3}]{\mathrm{CuI,\,L_2PdCl_2}} \mathrm{ArC{\equiv}CSiMe_3} \xrightarrow{\mathrm{NaOH}} \mathrm{ArC{\equiv}CH} \qquad 21$$

With alkyl and aryl copper compounds. The interaction of organocopper reagents and organic halides is one of the most important methods for the formation of carbon–carbon bonds, as this topic has been the subject of many reviews it will only be considered in outline here.[131]

The main types of organocopper compound are shown in Table 2. The reactivity of these reagents towards aryl halides is significantly lower than with alkyl halides, this necessitates the use of higher reaction temperatures. Since the decomposition of the organocopper reagent may become a major competing reaction to the coupling reaction the stability of the organocopper reagent is an important consideration. In general stability increases in the sequence $RCu < RCuL < MCuR_2$. R groups which contain β-hydrogen are generally unstable with respect to disproportion via the sequence of reactions in Scheme 12.[132]

$$\mathrm{CH_3CH_2Cu} \longrightarrow \mathrm{C_2H_4} + \mathrm{HCu}$$

$$\mathrm{CH_3CH_2Cu} + \mathrm{HCu} \longrightarrow \mathrm{C_2H_6} + 2\,\mathrm{Cu}$$

Scheme 12.

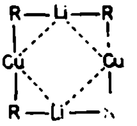
Clearly this process cannot occur in the absence of a β-H in the alkylcopper and such compounds have enhanced stability. It is hardly surprising therefore that most of the literature reports of reactions between aryl halides and RCu compounds involve R groups of this type for example, methyl, aryl or perfluoro.[131d] Although cross-coupling of aryl halides and lithium cuprates can be achieved at low temperatures by means of palladium or nickel catalysis.[151]

β-Elimination requires the metal to be coordinatively unsaturated and that the dihedral angle between the copper to carbon bond and the β-H to carbon bond approach zero.[137] The use of bulky chelating ligands which fulfil the dual role of filling empty metal orbitals and sterically inhibiting the β-elimination also lead to increased stability in organocopper compounds. These ideas have led to the synthesis of heterocuprates containing phosphido- and amido-ligands of enhanced stability.[133] The presence of an ortho chelating group in aryl copper compounds has a marked stabilising effect, for example, o-dimethylaminophenylcopper(I) is stable up to 120° in DMF.[134]

Table 2. Organocopper reagents

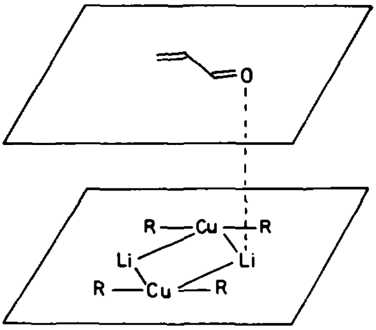
Reagent	Name
RCu, RCuLigand	Organocopper
$M_n[R_2Cu]_n$, $M_n[RR'Cu]_n$	Homocuprate
$M_n[RCuX]_n$	Heterocuprate

The most striking structural feature of organocopper reagents is their tendency to form aggregates.[135] The most common degree of aggregation is four, although hexameric and octameric species are known. The tetramers tend to have planar structures with bridging R groups.



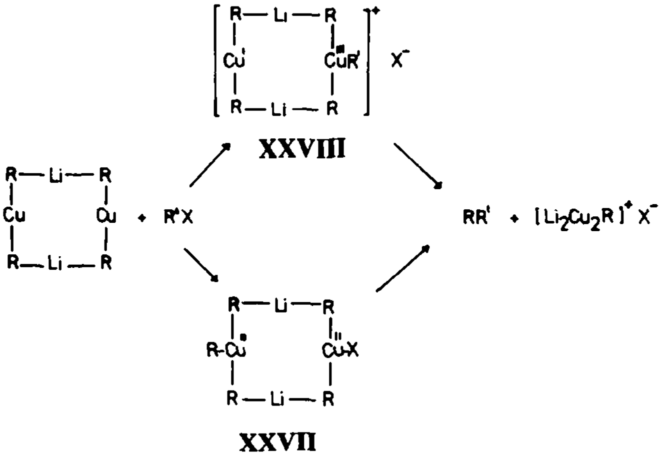
XXV

A recent theoretical study of organocopper compounds, organocuprates, and heterocuprates has shown that the planar structure is substantially more stable than a tetrahedral structure and that the R-groups in lithium cuprates are primarily bonded to the copper.[138] Each copper atom in lithium cuprate dimers has an empty 4p orbital which is perpendicular to the Cu_2Li_2 plane. It is suggested that these orbitals may be important in complexing with the substrate in coupling and addition reactions **XXVI.**[138]



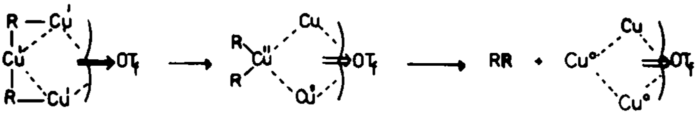
XXVI

Coupling between organocopper reagents and aryl halides is widely envisaged as a reaction sequence which involves oxidative addition to give either a copper(III) complex[139] (**XXVIII**), or copper(II)[140] complex **XXVII** followed by reductive elimination of product (Scheme 13).



Scheme 13.

Coupling may also be induced thermally, or by oxidation with one electron oxidants, such as O_2 or copper(II) salts, in which case substantial symmetrical coupling will accompany the cross coupling reaction.[125] Halogen exchange can also lead to symmetrical products.[141] Biaryl coupling in arylcopper tetramers can also be promoted by copper(I) triflate.[142] In this case an intermediate $Ar_4Cu_6(OT_f)_2$ species which contains an octahedral copper cluster is formed. The driving force for



Scheme 14.

the reaction is thought to arise from the preference of the strong electron attracting triflate ion for the copper(II) state and a sequence of reactions involving the partial structures shown in Scheme 14 is proposed as a route to biaryl.

There is almost universal acceptance that biaryl formation in the Ullmann reaction involves the interaction of an arylcopper species with an aryl halide,[143] although the actual mode of coupling is controversial.[144] The Majority of Ullmann couplings are carried out by conventional procedures.[143] However, the scope of Cohen's method,[145,157] for the coupling of 2-iodonitrobenzene to give 2,2′-dinitrobiphenyl using copper(I) triflate in acetone-acetonitrile containing ammonia has recently been investigated.[146]

Improved yields in the coupling of aryl iodides with 1,3-dinitrobiphenyls are obtained by replacing the copper(I) oxide used in the older method,[147] by the more basic copper(I) t-butoxide.[148] What is described as an ambient temperature Ullmann reaction is based on the cross-coupling of an ortholigand stabilised-aryl copper compound and an aryl halide was reported.[149] The reaction has been exploited as a key step in the synthesis of (±)-steganocin. This procedure is claimed to be superior to cross-coupling procedures based on nickel(O) or palladium(O).[150]

MECHANISTIC CONSIDERATIONS

Nature of the catalyst and solvent effects

A bewildering array of copper species have been used to promote the nucleophilic substitution of aryl halogen, with the copper being introduced into the system in the 0, + 1, + 2 or + 3 oxidation states. There are relatively few examples of the use of copper(III) complexes,[5] although there are several examples of the use of copper(II) complexes and an oxidant, these reactions are generally referred to as oxidative substitutions.[61]

It was noted in the previous section that in most of the reactions where copper(O) is the catalyst then it is necessary to have oxygen or some other oxidant in the system to generate the effective catalyst, which is considered by many workers to be a copper(I) species.[42,107,153] In many of the reactions catalysed by copper(II) complexes reduction to the copper(I) state appears to be necessary.[18,26–31,42,47,97] The mixed valence copper(I,II) complex **XII** which is formed from copper(II) acetate and trialkylphosphite has been shown to be a particularly effective phosphonation catalyst, although the mechanism of this reaction is discussed largely in terms of the copper(I) centre.[97]

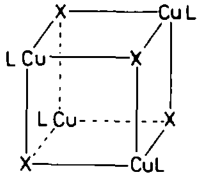
Copper assisted nucleophilic substitutions are subject to spectacular solvent effects and inhibitions by ligands. These points are interrelated since in many reactions the solvent fulfils the dual role of ligand and bulk solvent. An important feature of these reactions appears to be the formation of a coordination complex between the aryl halides and the copper. For this reason an important requirement of the copper compound is that it be coordinatively unsaturated or easily be made so. In the presence of a large excess of ligand the equilibria for complex formation will be driven towards coordinatively saturated species, such as $[CuL_4]^+$, which will inhibit the reaction. It is in this context that seemingly contradicting observations such as the inhibition of chloro-bromo exchange in aryl bromides by the addition of 4 mol equivalents of pyridine,[66] and the enhancement of the rate of exchange by the addition of 1 mol. equivalent of pyridine,[80,81] may be explained. An excess of anionic nucleophiles can cause similar problems which is presumably one of the major reasons why there are few efficient catalytic nucleophilic substitutions based on copper and alkali metal salts of nucleophiles. The formation of coordinatively saturated species will deplete the system of the catalytically active species, for purposes of illustration YCuL in Scheme 15.

In Scheme 15 only monomeric species are considered, however, copper(I) has a marked tendency to form oligomeric species.[166] For example, 1 : 1 copper(I) halide complexes with amines

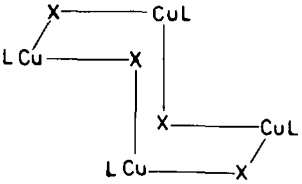
$$\begin{aligned}
&LCu + Y \underset{}{\overset{k_1}{\rightleftharpoons}} LCuY \\
&LCuY + Y \overset{k_2}{\rightleftharpoons} LCuY_2 \\
&LCuY_2 + Y \overset{k_3}{\rightleftharpoons} LCuY_3 \text{ etc.} \\
&ArX + LCuY \overset{k_4}{\rightleftharpoons} [(ArX)CuLY] \longrightarrow ArY + LCu + X
\end{aligned}$$

Scheme 15.

and phosphines are tetrameric with either cubane **XXIX** or step **XXX** structures.



XXIX



XXX

Oligomeric species are well known to be important intermediates in the coupling of organocopper and organocuprates with aryl halides.[131] There is evidence to suggest that oligomeric species may also be involved in copper assisted nucleophilic substitution. For example (i) a high CuI:nucleophile ratio is desirable in the copper assisted Gabriel reaction,[32] and in the reaction of aryl iodides with malonates.[113] (ii) cyanation of aryl halides with the coordinatively unsaturated, monomeric $Cu(CN)_2^-$ is less effective than with the oligomeric CuCN,[119,121] and LCuCN (L = pyridine,[80] triphenylphosphine.[152]) (iii) $Cu_3(OAc)_5(P(OEt)_3)_2$, **XII**, is more efficient in the phosphonation of aryl halides than the monomeric solution species of the type $Cu(OAc)(P(OEt)_3)$ bipyridyl.[97]

These oligomeric species are prone to dissociation by interaction with solvents and ligands. For example, phosphonation of aryl halides by the complex $Cu_3(OAc)_5(P(OR)_3)_2$ **XII** occurs best in ethanol and less efficiently in THF, which is known to cause dissociation of the trimer into copper(II) acetate and $Cu^IOAc(P(OR)_3)_2$.[97]

It is also likely that copper free nucleophiles do not participate in these reactions and hence the solvent will exert a marked influence if it facilitates the production of cationic complexes of the type $[CuL_4]^+X^-$ (L = solvent, X = nucleophile). The reactions of bromoperfluoroaromatics shown in Scheme 8 nicely illustrate this point.[76]

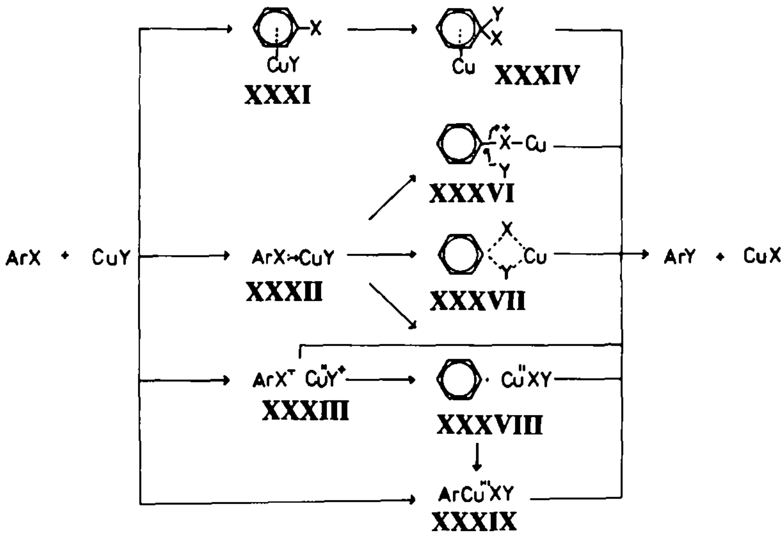
Kinetics and mechanism

The kinetics of copper promoted nucleophilic aromatic substitution was reviewed by Shein in 1976.[154] Two classes of reaction were recognised. The first comprise the reactions in which copper is both the catalyst and nucleophilic reagent, these reactions generally exhibit second order kinetics, being first order in both aryl halide and copper compounds, although there are some examples which show deviations.[66,97] The second class of reactions are those in which copper is catalytic, these reactions often show fractional orders which were explained in terms of different ratios of K_1 and K_4 in Scheme 15.[154]

As discussed above an important feature of these copper promoted substitutions appears to be the formation of a complex between the aryl halide and copper. If this assumption is valid then the remaining mechanistic problems are associated with the structure of such an intermediate and its mode of decomposition into products. Possible pathways are shown in Scheme 16.

The problem of the same starting materials giving rise to identical products by several different pathways is quite general in nucleophilic aromatic substitution and has led Shein to suggest that the classification of the mechanism of substitution based on reaction orders is inadequate.[155] He suggests that mechanisms should be classified in terms of the type of intermediates in the reaction.

There have been several reports of the use of the Hammett equation to evaluate the effect of ring substituents on the rate of reaction. All of the reactions studied give low positive values of

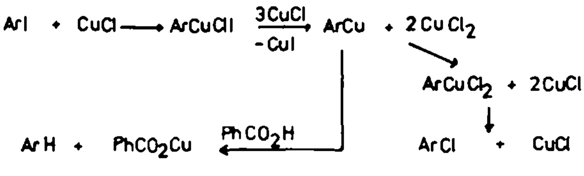


Scheme 16.

the reaction constant ρ; values lying in the range $+0.1$ to $+1.1$.[46,86,167,168] The positive ρ values indicates the nucleophilic nature of the reactions, however, the values are low compared with those for uncatalysed nucleophilic substitutions which proceed by nucleophilic addition.[46] Low ρ values have been reported to be characteristic of reactions in which there is a bridge which weakly transmits the electron withdrawing effect of the substituent between the reaction centre and the aromatic ring containing the substituent.[46] These arguments are considered to support the formation of a complex between the aryl halogen and copper, **XXXII** (Scheme 16) the ease of formation of which should follow the order of polarisability of the halogen. The order of halogen displacement I > Br > Cl > F and the ortho effect of chelating groups is taken as further evidence in support of this and against the involvement of π-complex intermediates such as **XXXI** (Scheme 16).[46]

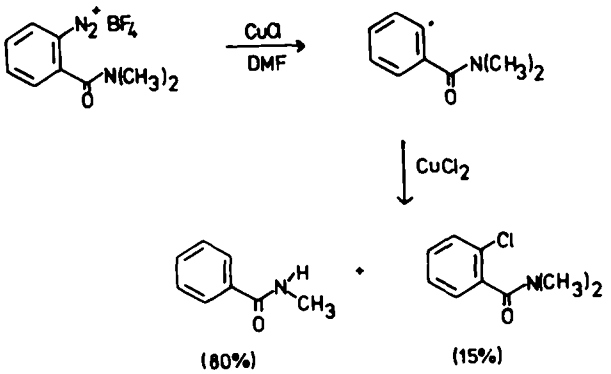
However, ρ values similar to those reported for copper promoted nucleophilic displacements are observed for the polarographic reduction of aryl halides in DMF (ArI $= +0.31$; ArBr $\rho = +0.57$, ArCl $\rho = +0.81$).[164] These data were considered to rule out the involvement of intermediates which require the development of positive charge at the carbon centre (S_N1 type) and are supportive of mechanisms which involve carbanionic (S_N2), radical or radical anions; in the context of copper promoted reactions intermediates of the type **XXXVII**, **XXXVIII** or **XXXIII**. Although intermediates of types **XXXVIII** and **XXXIII** are also known to be involved in oxad. reactions of transitions metals to give intermediates of type **XXXIX**.[7]

As noted earlier reductive dehalogenation to arene and coupling to give biaryls often accompanies copper assisted nucleophilic substitution. A mechanism which involves both organocopper(I) and organocopper(III) intermediates was proposed by Cohen,[156] (Scheme 17) to explain the presence of reductive dehalogenation products formed during the chlorine–iodine exchange with 2-iodo-N,N-dimethylbenzamide in the presence of benzoic acid.



Scheme 17.

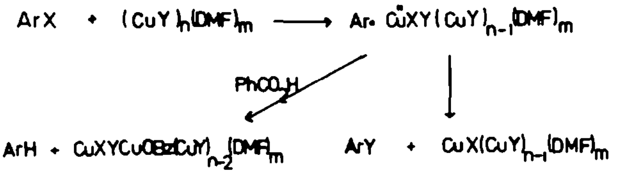
The ratio of ArH to ArCl in this reaction could be increased by the addition of benzoic acid and reduced by adding $CuCl_2$. Radical pathways to ArH were discounted on the grounds that the ortho-N,N-dimethylbenzamide radical readily undergoes intramolecular hydrogen abstraction to



Scheme 18.

give N-methylbenzamide and formaldehyde. These products are not detected in the exchange reaction but are the major products from the reaction of the N,N-dimethylbenzamide radical with excess copper(II) (Scheme 18).

The involvement of organocopper(I) intermediates in copper assisted nucleophilic displacements was criticised by Van Koten and coworkers,[158] who demonstrated that organocopper(I) compounds give rise to substantial amounts of biaryl in addition to arene and substitution products. These workers proposed an alternative route to substitution and reductive dehalogenation which involves the formation of aryl radicals by single electron transfer from an oligomeric copper complex (Scheme 19).[158]



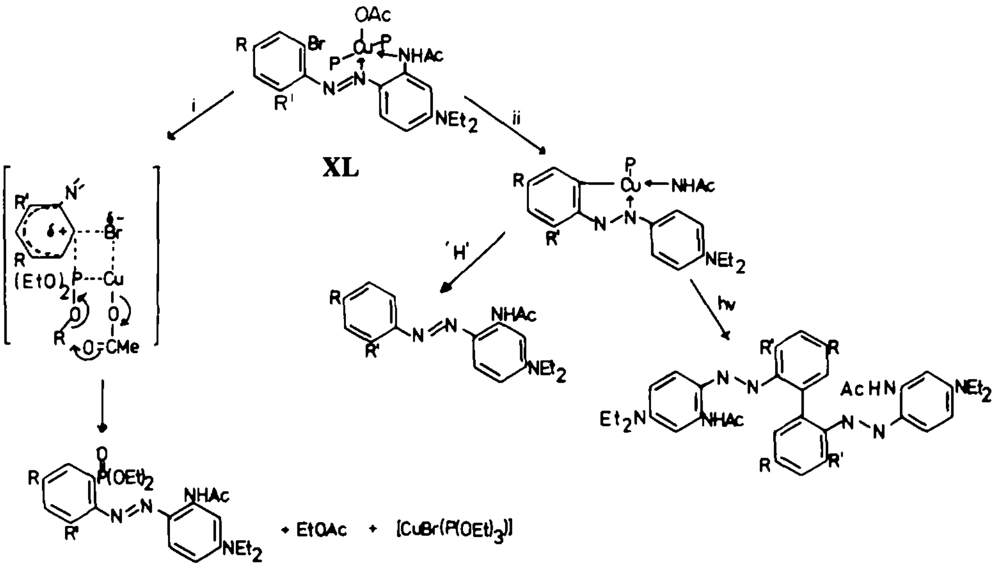
Scheme 19.

Liedholm[85] considered that square planar organocopper(III) intermediates are inconsistent with her observations of a rate acceleration correlated with increasing van der Waals radius of the substituent ortho to the reaction centre and the large negative entropies of activation in halogen exchange reactions. Although it is well known that ortho substituents have a marked stabilising effect on the square planar aryl complexes of Ni, Pd and Pt.[160] Direct evidence for organocopper(III) intermediates has been obtained in reactions of alkyl radicals with copper(II),[163] and organocopper(III) compounds, formed by the addition of alkyl radicals to copper(II) salts, are known to readily undergo reductive elimination (eqn 22).

$$CH_3^{\bullet} + Cu(OAc)_2 \longrightarrow CH_3Cu(OAc)_2 \longrightarrow CH_3OAc + \dot{C}uOAc \qquad 22$$

There has been a substantial increase in the number of reports of copper(III) complexes in recent years, some of these have an important biochemical role and although copper(III) is often regarded as a potent oxidant some of these complexes have E° values as low as 0.37 volts.[161] It is also interesting that as long ago as 1931 Kharasch reported that dichlorophenylgold(III) readily undergoes reductive elimination to form chlorobenzene in high yield.[159]

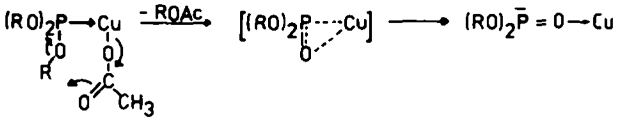
As noted above the study by Connor and coworkers[97] of the copper promoted phosphonation of o-bromodiarylazo compounds provides good evidence that all three products of the reaction (phosphonate, arene and biaryl) originate from a common intermediate and that radicals are involved in the formation of the arene and biaryl but are not involved in the formation of the phosphonate. These workers propose a mechanism which involves the initial formation of a chelate complex between the aryl halide and the copper phosphite complex XL, Scheme 20, which may rearrange via a concerted pathway which leads to phosphonate, (i) Scheme 20, or via an



Scheme 20.

organocopper(I) compound, (ii) Scheme 20, which in the presence of light leads to biaryl and on interaction with protonactive compounds leads to arene.

The rate of formation of phosphonate in these systems is unaffected by radical scavengers or by reaction in the dark, whereas the formation of biaryl is totally inhibited and arene formation is substantially reduced both at the expense of phosphonate under these conditions. Since all of the displaced bromine appears in CuBrP(OEt)$_3$ and the displaced ethyl group in ethyl acetate the route to phosphonate is thought to involve nucleophilic attack by acetate ion on coordinated phosphite to yield a phosphonate which undergoes coordination isomerism to generate a negative centre at phosphorus suitable for attack at a carbocationic centre on the ring (Scheme 21).



Scheme 21.

Although it is noteworthy that o-bromodiarylazo compounds are known to react under mild conditions with tertiaryphosphines and copper(II) acetate to give phosphonium salts.[99] This suggests that the development of a negative centre at phosphorus is not an essential prelude to the substitution of aryl halogen. The involvement of an aryl copper(I) complex (step ii, Scheme 20) in the route to biaryl and arene was proposed following the observation that the reaction between such a compound, formed by reaction of CuX(X = Br,I,OAc) and **VII** (X = Li), and aryl iodides yields reductive dehalogenation and biaryl products.[161] However, the route to reduction and biaryl (Scheme 20), presumably must involve an electron transfer from copper to aryl halide stage, which is inhibited in the presence of scavengers. It is interesting that the most effective reagent for the phosphonation of o-bromodiarylazo compounds is the mixed valence copper(I)–copper(II) complex **XII**. The addition of copper(II) compounds have also been shown to have beneficial effects in the reactions of haloanthraquinones with amines,[26–31] and in certain industrial processes.[10,169] This may indicate that mixed valence species are also involved in these reactions, although the precise role of copper(II) is not known. As the trimeric mixed valence species (**XII**) leads to a substantial reduction in radical derived products compared with the copper(I) complexes **XVI** and **XVII** one may speculate that the copper(II) atoms function as electron acceptors and thereby inhibit the formation of radicals. It is interesting that solvents which cause dissociation of **XII** also lead to a substantial increase in reductive dehalogenation and biaryl coupling this indicates that it is necessary for the copper(I) and copper(II) atoms to closely approach each other to be effective in reducing radical formation.

The non-radical pathways for copper assisted nucleophilic substitution are those involving either bridge intermediates, **XXXVII** Scheme 16, or concerted oxidative addition-reductive elimination via a copper(III) intermediate **XXXIX**. The ρ values (*ca* 0.6) observed in several copper assisted substitutions of aryl bromides are low compared with values of $+4.4$ for the oxidative addition of aryl bromides to the more electron rich Ni(O) complexes.[165] This suggests that aryl copper(III) intermediates are not involved in these nucleophilic substitutions.

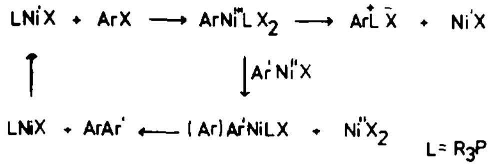
However, in view of the large number of nucleophilic substitutions promoted by copper complexes, the marked effects that solvents and ligands can have on the redox potentials of copper and the observations that radicals can be readily generated in these systems it is not unreasonable to expect that a small change in the reaction conditions may lead to a change in mechanism.

OTHER METAL ASSISTED NUCLEOPHILIC SUBSTITUTIONS

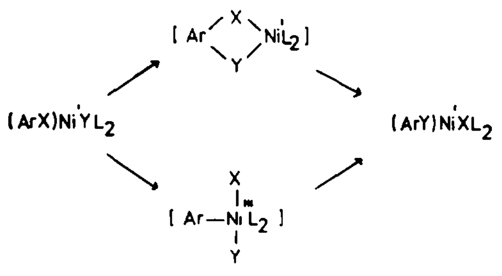
Over the past decade there has been a large increase in the use of metals other than copper in nucleophilic aromatic substitution. The nucleophilic substitution of π-arene metal complexes was mentioned earlier.[2] Metal catalysed cross-coupling reactions of organometals and organic halides has been the subject of several recent reviews.[7,150,170] Halogen exchange is promoted by nickel,[171,172,181,184] and cobalt complexes.[171] The cyanation of aryl halides is catalysed by nickel,[173-5] palladium,[176,177] and cobalt complexes.[178]

The reaction of aryl halides with (i) amines is catalysed by nickel,[171] cobalt,[171] and rhodium complexes;[179] (ii) phosphines is catalysed by nickel,[99,180,182,184] and palladium complexes;[185] (iii) phosphites is catalysed by nickel;[91,186,187] (iv) alkyl and aryl thiolates are catalysed by nickel,[183,189] and palladium complexes,[188,189] and (v) phenoxides is catalysed by nickel complexes.[171] Many of these reactions occur under much milder conditions than with copper compounds.

The mechanism of formation of aryl phosphonium salts and biaryls catalysed by nickel complexes has been studied in some detail by Kochi and Tsou.[180] They found that the effective catalyst is a nickel(I) species which can be generated from nickel(O) or nickel(II) precursors by electron transfer to aryl halide. The reaction proceeds by a chain mechanism in which nickel(I) and nickel(III) species are the reactive intermediates, Scheme 22. Nickel(I) intermediates are also the catalytically active species in the halogen exchange reactions promoted by nickel complexes.[172] However, halogen transfer by a bridged intermediate is considered to be a more reasonable mechanism that the alternative involving oxidative addition and reductive elimination (Scheme 23).[172]



Scheme 22.



Scheme 23.

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