COPPER-PROMOTED REACTIONS IN AROMATIC CHEMISTRY

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General features

Copper and its compounds are outstanding within the transition series for the variety and value of their applications as reagents or catalysts for organic reactions. The development of these processes has been largely empirical and their mechanisms are not well understood. This Review is confined to aspects of copper chemistry encountered in aromatic reactions, and is particularly concerned with recent observations in this area. Less attention is paid to long-established features which have been described in other reviews; these include accounts of the Ullmann method of biaryl synthesis,[1] the Sandmeyer reaction,[2,3] and some other applications in nucleophilic aromatic substitution processes.[4] To systematise the diverse effects of copper described in the recent literature, they are grouped in accordance with the change undergone by the aromatic compound, *i.e.*, as reduction, oxidation, substitution, or ring-enlargement processes. The following are examples:

Reductions:

$$2\mathrm{ArHal} + 2\mathrm{Cu} \rightarrow \mathrm{Ar{\cdot}Ar} + 2\mathrm{Cu}^{+} + 2\mathrm{Hal}^{-}$$
$$2\mathrm{ArN_2}^{+} + 2\mathrm{Cu}^{+} \rightarrow \mathrm{Ar{\cdot}Ar} + 2\mathrm{Cu}^{2+} + 2\mathrm{N_2}$$
$$\mathrm{ArHal} + \mathrm{XH_2} \xrightarrow{\mathrm{Cu^{I}}} \mathrm{ArH} + \mathrm{HHal} + \mathrm{X}$$

Oxidations:

$$2\mathrm{Ar^{-}MgX^{+}} + 2\mathrm{Cu}^{2+} \rightarrow \mathrm{Ar{\cdot}Ar} + 2\mathrm{Cu}^{+} + 2\mathrm{MgX}^{+}$$
$$\mathrm{ArNH{\cdot}NH_2} + 2\mathrm{Cu}^{2+} \rightarrow \mathrm{ArH} + 2\mathrm{Cu}^{+} + 2\mathrm{H}^{+} + \mathrm{N_2}$$
$$\mathrm{ArH} + \mathrm{O_2} \xrightarrow{\mathrm{Cu^{II}}} \mathrm{ArOH}\ \text{etc.}$$
$$2\mathrm{ArH} + 2\mathrm{Cu}^{3+} \rightarrow \mathrm{Ar{\cdot}Ar} + 2\mathrm{Cu}^{2+} + 2\mathrm{H}^{+}$$
$$\mathrm{ArH} + \mathrm{Br}^{-} + 2\mathrm{Cu}^{2+} \rightarrow \mathrm{ArBr} + 2\mathrm{Cu}^{+} + \mathrm{H}^{+}$$

Replacements:

$$\mathrm{ArHal} + \mathrm{CuX} \rightarrow \mathrm{ArX} + \mathrm{CuHal}$$
$$\mathrm{ArHal} + \mathrm{HX} \xrightarrow{\mathrm{Cu^{I}}} \mathrm{ArX} + \mathrm{HHal}$$
$$\mathrm{ArN_2}^{+} + \mathrm{X}^{-} \xrightarrow{\mathrm{Cu^{I}}} \mathrm{ArX} + \mathrm{ArX} + \mathrm{N_2}$$

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[1] P. E. Fanta, *Chem. Rev.*, 1946, **38**, 139; 1964, **64**, 613.

[2] W. A. Cowdrey and D. S. Davies, *Quart. Rev.*, 1952, **6**, 358.

[3] K. H. Saunders, "The Aromatic Diazo-compounds and their Technical Applications," Edward Arnold and Co., London, 1949.

[4] J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, 1951, **49**, 273.

It will be seen that in some cases the copper species undergoes cheimcal change and in other cases its function is catalytic. Thus, some aromatic reductions involve electron loss in the copper, $Cu^0 \rightarrow Cu^I$ or $Cu^I \rightarrow Cu^{II}$, and some oxidations involve electron gain, $Cu^{II} \rightarrow Cu^I$ or, occasionally, $Cu^{III} \rightarrow Cu^{II}$. In other instances a copper species catalyses processes in which, *e.g.*, oxygen is the oxidant, or an alcohol or alkoxide is the reductant. Likewise, in substitution processes, copper species may undergo ligand exchange with the substrate, whilst in other cases a copper catalyst and a nucleophil are separate components of the reaction system. These are essentially practical distinctions, since catalysis may in fact involve transient chemical change in the copper, *e.g.*, by the formation of intermediate complexes, or by the operation of oxidation–reduction cycles:

$$Cu^I - e \rightarrow Cu^{II} \rightarrow Cu^I + e$$

Before particular reactions are discussed, attention is drawn to the following general features of aromatic reactions involving copper species:

(*a*) The literature is largely concerned with chemical changes in organic molecules and there is a dearth of information, qualitative or quantitative, concerning changes in the copper. To a varying extent, copper is likely to be present at more than one oxidation level, proportions of which may alter during reaction. This could be due to initial heterogeneity, to oxidation–reduction processes, or to disproportionation

$$2Cu^I \rightleftharpoons Cu + Cu^{II}$$

(*b*) The copper ions undergo complex-formation with molecules or anions in the reaction system. It is therefore understandable that copper-assisted reactions are frequently very variable in rate, and are sometimes completely inhibited, depending, *e.g.*, upon what anions, reagent, or solvent molecules, or specific complexing agents are present in the system to compete as ligands for the metal.

(*c*) Copper species are effective towards a limited range of atoms or groups in aromatic molecules; these are mainly halogen atoms, diazonium-salt groups, and some sulphur-containing functional groups. There is, in addition, increasing evidence that copper has a marked capacity for facilitating hydrogen transfer from a wide range of donor molecules to specific acceptors.

(*d*) Substituent effects in copper-promoted aromatic reactions may differ from those in related reactions not involving copper; this needs further elucidation. When, *e.g.*, the group Y in a substrate C_6H_4XY is an unsaturated function, such as NO_2 or CO_2H, the response of X is often high, particularly if it is in an *ortho*-position to Y.

(*e*) Both heterolytic and homolytic mechanisms have been suggested, but it is often difficult to establish that a reaction is of one form or the other. A complication is the possibility of interconversion between organic intermediates of ionic and radical type, by processes such as $R\cdot + Cu^{2+} \rightarrow R^+ + Cu^+$

(*f*) Special problems arise when reactions occur at interfaces between solid copper species and liquid organic media. In such heterogeneous systems, reaction rates or yields of products tend to be rather poorly reproducible and to be affected by changes in agitation conditions, and changes in the physical or chemical character of the surface.

The commonest reagents thus employed are copper metal and cuprous oxide. The former, whether employed, *e.g.*, as "copper bronze" or as the powder precipitated from a copper(II) salt solution, may be contaminated with other metals, oxygen, anions, or organic material. For various purposes, *e.g.*, Ullmann syntheses,[1] metal from prescribed sources has been recommended, or preliminary treatments have been advocated, such as washing with organic solvents, or activation of the surface with iodine. In the case of cuprous oxide, the Cu_2O content of a sample of typical laboratory-grade reagent may be no higher than about 90%; it will probably also contain substantial amounts of CuO, and may be contaminated with small amounts of moisture, cationic and anionic species, and organic material. A precipitation method has been used by some investigators to prepare cuprous oxide used in diazonium-salt reactions.[3] Samples of the oxide prepared from the pure elements prove to be non-stoicheiometric, with an excess of oxygen atoms in the lattice.[5] There are large departures from the stoicheiometric proportion in surface layers of oxide made by reaction of oxygen with copper films.[6] The consequences of these lattice irregularities for the catalysis of reactions in the gaseous phase have still to be clarified, and their effects on liquid-phase reactions are even more obscure.

The relative energies of the oxidation states of the metal, and the type and stability of the complexes which it forms in its different oxidation states are highly relevant to copper-promoted aromatic reactions. These features of the inorganic chemistry of the element are briefly surveyed in the next section.

Inorganic chemistry of copper

Thermodynamics.—Copper, atomic number 29, has the electronic configuration $KL\ 3s^2,3p^6,3d^{10},4s^1$. The first three ionisation potentials are 7·72, 20·29, and 36·83ev. The relatively high ionisation potential, together with a large sublimation energy, contribute to the "noble" character and resistance to oxidation of the metal. The principal oxidation states are +1 and +2, with the +3 state known for a few complexes, *e.g.*, K_3CuF_6. The second ionisation potential of copper is large compared with that of any element in the same Period, from calcium (11·87) to nickel (18·15ev), and

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[5] M. O'Keeffe and F. S. Stone, *Proc. Roy. Soc.*, 1962, *A*, **267**, 501.

[6] C. M. Quinn and M. W. Roberts, *Trans. Faraday Soc.*, 1964, **60**, 899.

for this reason copper(I) is more stable to oxidation than the other transition metals of the Period in their +1 oxidation states.

The relative stability of the first three oxidation states, 0, +1, and +2, is very sensitive to change in environment. The standard electrode potentials of copper in aqueous solution are Cu/Cu^{I}, +0·522v; Cu/Cu^{II}, +0·345v; the large heat of hydration of copper(II), −507kcal., compared with that of copper(I), −139kcal., compensates for the higher second ionisation potential to make the hydrated copper(II) ion the more stable state in aqueous solution. All soluble, simple copper(I) salts disproportionate in water by the reaction $2Cu^{I}_{aq} \rightarrow Cu^{0} + Cu^{II}_{aq}$, with the disproportionation constant $K = 1{\cdot}2 \times 10^{6}$ at 25°. In the presence of ligands, for which the metal in its two oxidation states has different affinities, the disproportionation constant varies greatly; thus, in aqueous 1,2-diaminoethane, which can chelate copper(II) but not copper(I), $K = 10^{5}$, but in aqueous ammonia, $K = 2 \times 10^{-2}$. The latter relationship is reflected in the reaction

$$Cu(NH_3)_4{}^{2+} + Cu \rightarrow 2Cu(NH_3)_2{}^{+}$$

Copper(I) tends to form thermodynamically stable complexes with polarisable ligands or π-accepting ligands. The stability of copper(I) halide complexes in aqueous solution increases with increasing atomic number of the halogen, and copper(I) is therefore a so-called "class *b*" ion.[7] Copper(II) halides have the reverse order of stability and copper(II) is a "class *a*" ion. Copper(I) forms complexes with carbon monoxide, cyanide ion, alkenes,[8] alkynes,[9] and in special circumstances aromatic nuclei,[10] all these ligands having empty π*-orbitals capable of taking part in synergic bonding, *i.e.*, σ-donation from the ligand to the metal ion and π-donation from the *d*-orbitals of the metal to the π*-orbitals of the ligand. It has been suggested[7] that similar bonding is involved in the "class *b*" halide complexes, with the empty *d*-orbitals of the halide ions as π*-orbitals, but it also has been suggested[11] that polarisation by the electronegative copper(I) is more important. Such discussions tend to obscure the fact that the "class *b*" metal–halide bond strengths in the gas phase increase with decreasing atomic number of the halogen. However the increase is much less than in "class *a*" metal halides and so in aqueous solution the free energy of hydration of, for example, the chloride ion, dominates and reverses the usual "class *a*" stability order. The stability of copper(I) complexes has been little studied, either in aqueous or non-aqueous solution, and would repay investigation. Copper(II), on the other hand, has been extensively studied and it is evident that, of all bivalent ions of the first transition Period, copper(II) usually forms the most thermodynamically stable complexes. This has been

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[7] S. Ahrland, J. Chatt, and N. R. Davies, *Quart. Rev.*, 1958, **12,** 265.

[8] R. M. Keefer and L. J. Andrews, *J. Amer. Chem. Soc.*, 1949, **71,** 1723.

[9] G. E. Coates, "Organo-metallic Compounds," Methuen and Co., London, 2nd edn., 1960, p. 352.

[10] R. W. Turner and E. L. Amma, *J. Amer. Chem. Soc.*, 1963, **85,** 4046.

[11] R. J. P. Williams, *Proc. Chem. Soc.*, 1960, 20.

expressed[12] in the Irving–Williams series of complex-ion stabilities: $Mn^{2+} < Fe^{2+} < Co^{2+} < Ni^{2+} < Cu^{2+} > Zn^{2+}$. The interpretation of this sequence is still open to question.

Stereochemistry.—When associated with ligands of low polarisability, or ligands which have no empty π-orbitals, copper(I) usually has the co-ordination number two, as in $Cu(NH_3)_2^+$, and forms two linear bonds, which can be described in terms of either *sp*-, or *sd*-hybrid orbitals.[13] With π-bonding or polarisable ligands, the co-ordination number is variable, though usually four, and tetrahedral stereochemistry is observed. Copper(II), on the other hand, has either (*a*) a co-ordination number of six with a distorted octahedral arrangement, usually with four short bonds and two long bonds, owing to either Jahn–Teller distortion or lack of spherical symmetry of the d^9 ion, or (*b*) a co-ordination number of four, with a square-planar arrangement, which can be considered as an extreme case of a tetragonally distorted octahedron, involving complete removal of two *trans* ligands. Copper(II) is only tetrahedral in a few complexes, *e.g.*, K_2CuCl_4. The difference in stereochemistry displayed by the two oxidation states often affects the Cu^I/Cu^{II} redox potential. This is illustrated by some observations[14] on complexes of copper(I) and (II) with bipyridyls and *o*-phenanthrolines. Substituents in the 6,6′-positions in the 2,2′-bipyridyls increase the oxidation potential, *i.e.*, increase the relative stability of the copper(I) state, thereby reflecting the smaller sensitivity of tetrahedral copper(I) to steric interaction as compared with that of square-planar copper(II).

Kinetics.—It might be expected that the kinetic stability of copper(I) complexes, like other d^{10}-complexes,[15] would approximately follow their order of thermodynamic stability. Even so, these complexes are labile, perhaps because of the spherically symmetric ion resulting from the filled *d*-subshell. The rate of the reaction[16] between the species $Cu(CN)_2^-$ and $^*CN^-$ was such that exchange was complete in 2 minutes, even though the assocation constant, β_2, of $Cu(CN)_2^-$ is $\sim 10^{24}$.

The rates of formation and the exchange rates of complex copper(II) ion with most ligands are very fast. Thus the rate of exchange of water with the aquated ion has[17] a first-order rate constant of 10^8 sec.$^{-1}$, and even exchange with a chelating ligand, exemplified by reaction of the species $Cu(en)_2^{2+}$ with isotopically labelled 1,2-diaminoethane,[18] is 90% complete in 3 seconds at 0°. The lability of most copper(II) complexes results from

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[12] H. Irving and R. J. P. Williams, *J.*, 1953, 3192.

[13] L. E. Orgel, "Introduction to Transition-Metal Chemistry," Methuen and Co., London, 1960, p. 66.

[14] B. R. James and R. J. P. Williams, *J.*, 1961, 2007.

[15] H. G. Hertz, *Z. Electrochem.*, 1961, **65**, 36.

[16] A. C. MacDiarmid and N. F. Hall, *J. Amer. Chem. Soc.*, 1954, **76**, 4222.

[17] M. Eigen, *J. Pure Appl. Chem.*, 1963, **6**, 97; R. E. Connick and E. D. Stover, *J. Phys. Chem.*, 1961, **65**, 2075.

[18] D. G. Popplewell and R. G. Wilkins, *J.*, 1955, 4098.

the weak bonding and ease of replacement of the two axial ligands. Electron exchange between copper(I) and copper(II)[19] is very fast, with a rate constant 5×10^7 $\text{M}^{-1}\text{sec.}^{-1}$, at least in the presence of halide ions, which form a bridge between the two cations, thereby facilitating electron transfer.

Catalysis by Copper Compounds.—Copper(I), by forming complexes with aromatic nuclei, alkenes, alkynes, and aryl halides, may so perturb the molecule that a different rate of reaction or distribution of products from that observed in the absence of the metal ion may result. Similarly, perturbation by metal ions such as copper(II), functioning as Lewis acids, has been used to explain their catalysis[20] of, *e.g.*, the bromination of β-diketones. The small differences in energy between the first three oxidation states, 0, +1, and +2, has an important effect in the use of copper and its compounds as catalysts. Thus, when the metal has been converted into a particular oxidation state, some oxidant or reductant may cause reversion of the metal ion to its initial oxidation state, and so the active ion may be continuously regenerated. Both copper(I) and copper(II) are suited to catalyse numerous organic reactions because of their ability to form complexes with a wide variety of ligands, and because formation and dissociation of the complexes can occur very rapidly.

Reduction processes

The reactions to be discussed are (i) additive hydrogenations, $X + H_2 \rightarrow XH_2$, (ii) reductive coupling, $2ArX \rightarrow Ar.Ar$, (iii) substitutive reduction, $ArX \rightarrow ArH$. Examples of copper-promoted reactions of types (ii) and (iii) are found among halides, certain sulphur compounds, and diazonium salts.

(*a*) **Additive Hydrogenation.**—For heterolytic gas-phase hydrogenation, the catalytic activity of copper is much inferior to that of many other transition metals.[21] On the other hand, the study of homogeneous hydrogenation in the liquid phase[22] arises from Calvin's discovery[23] that solutions of some copper(I) salts activated molecular hydrogen as a reductant for some inorganic species and for *p*-benzoquinone; *e.g.*, the latter absorbed about 1 mol. of hydrogen at 100° in quinoline containing copper(I) acetate.[23,24] Silver and mercury were also catalysts for some homogeneous hydrogenations, and the utility of copper with respect to organic substrates is now known to be greatly exceeded by that of certain complexes of other

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[19] H. M. McConnell and H. E. Weaver, *J. Chem. Phys.*, 1956, **25**, 307.

[20] F. Basolo and R. G. Pearson, "Mechanism of Inorganic Reactions," John Wiley and Sons, New York, 1958, p. 333.

[21] C. G. Bond, "Catalysis by Metals," Academic Press, New York, 1962.

[22] J. Halpern, *Quart. Rev.*, 1956, **10**, 463; *Adv. Catalysis*, 1959, **11**, 301.

[23] M. Calvin, *Trans. Faraday Soc.*, 1938, **34**, 1181; *J. Amer. Chem. Soc.*, 1939, **61**, 2230.

[24] S. Weller and G. A. Mills, *J. Amer. Chem. Soc.*, 1953, **75**, 769; L. W. Wright and S. Weller, *ibid.*, 1954, **76**, 3345.

transition metals.[25] Indeed, *p*-benzoquinone appears to be the only organic compound for which copper has been demonstrated to function as a homogeneous-hydrogenation catalyst; even tetrachloro-*p*-benzoquinone failed to be reduced, owing, it was suggested, to strong bonding with copper, preventing access of hydrogen to the metal.[23] In spite of this severe limitation, the reduction of benzoquinone is of interest for this Review as an example of copper-catalysed hydrogen transfer, discussed in Sections (*e*) and (*f*). In this respect it represents an extreme case, molecular hydrogen being a donor of low activity and high specificity, compared with some of those donors which are highly effective for substitutive reduction processes of type (iii) discussed in later Sections. Moreover, present experience suggests[26] that donors which are effective for these copper-catalysed substitutive reductions are not assisted by copper catalysis in the additive reduction of unsaturated compounds, such as quinones.

Homogeneous hydrogenation also provides a good example of some of the generalisations which were made (p. 96) concerning copper-promoted reactions. Thus, reduction systems may contain the species copper(II), dimeric or monomeric copper(I), and copper(O), among which copper(I) species appear to be the most effective; the rate of reaction is highly dependent upon the nature of anions, solvent, or complexing agents in the system; reduction is considered to proceed by a heterolytic or homolytic route, depending on circumstances.[22,27] The following representation of the heterolytic process shows transfer of hydride ion to copper, and assistance by an organic basic solvent, which combines with a proton:

$$\begin{gathered}
\mathrm{Cu^{2+} + H_2 + B \rightleftharpoons CuH^+ + BH^+} \\
\mathrm{CuH^+ + Cu^{2+} + B \rightarrow 2Cu^+ + BH^+} \\
\mathrm{Cu^+ + H_2 + B \rightleftharpoons CuH + BH^+} \\
\mathrm{O{:}C_6H_4{:}O + CuH + BH^+ \rightarrow HO{\cdot}C_6H_4{\cdot}OH + Cu^+ + B}
\end{gathered}$$

(*b*) **Reductive Coupling of Halides.**—The production of biaryls[1] by the Ullmann coupling process

$$\mathrm{2ArHal + 2Cu \rightarrow Ar{\cdot}Ar + 2CuHal}$$

dates from F. Ullmann's investigations in 1901. The term "Ullmann reaction" is also applied to copper-catalysed condensations of aryl halides with phenols or amines (p. 122) which he investigated later. The coupling reaction is frequently a good method for preparing symmetrical biaryls, and is sometimes successful for conversions of mixed halides into unsymmetrical biaryls; it has been applied to some hundreds of mono-

[25] J. Halpern, J. F. Harrod, and B. R. James, *J. Amer. Chem. Soc.*, 1961, **83**, 753; J. Kwiatek, I. L. Mador, and J. K. Seyler, *ibid.*, 1962, **84**, 304; R. D. Gillard, J. A. Osborn, P. B. Stockwell, and G. Wilkinson, *Proc. Chem. Soc.*, 1964, 284.

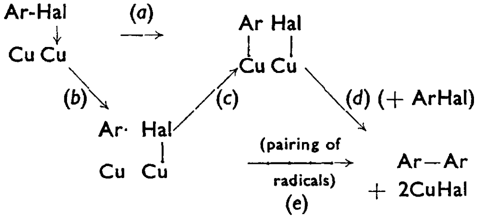
[26] R. G. R. Bacon, S. C. Rennison, and O. J. Stewart, unpublished investigations.

[27] M. Parris and R. J. P. Williams, *Discuss. Faraday Soc.*, 1960, **29**, 240; W. J. Dunning and P. E. Potter, *Proc. Chem. Soc.*, 1960, 244.

cyclic or polycyclic aryl halides and heteroaromatic halides.[1] It can be used in the ferrocene series.[28]

All these preparations constitute a subdivision of the broader area of halide–metal interactions, which have often been discussed as examples of homolytic processes; on the other hand, it has long been recognised that ionic intermediates may also be involved.[29] There have been advocates both of a homolytic interpretation[30,31] of the Ullmann coupling reaction, and of a heterolytic interpretation.[1,32] Several features of the process were discussed by Forrest,[33] who examined substituent effects for normal and abnormal courses of reaction in symmetrical and unsymmetrical Ullmann coupling. One of his investigations[33f] concerned the relative ease of formation of symmetrical or unsymmetrical biaryls, Ar.Ar or Ar.Ar′, in mixtures containing a reactive halide, ArHal, and a less reactive halide, Ar′Hal; he considered that the results were best explained by a heterolytic reaction mechanism.

If depicted as in discussions of reactions of gaseous alkyl halides on metal surfaces,[34] decomposition of liquid aryl halide on a copper surface would follow the path (*a*) shown in the annexed scheme; chemisorption here involves association with the metal through the halogen atom, and accession of two electrons from the lattice, giving a copper halide and copper aryl. The latter might then react heterolytically with further aryl halide, as in (*d*) to give the biaryl. The copper(I) can serve to activate the halogen of the aryl halide as in copper-catalysed substitutions. Alternatively, the bond-breaking process occurring in chemisorption might involve successive accession of single electrons, as in (*b*) and (*c*), giving an intermediate aryl radical; the pairing of radicals might then also give the biaryl, as in (*e*).



This mechanistic distinction may however be too rigid, since the postulated copper aryl is a thermally unstable species and can be regarded as a source of either aryl radicals or ions:

$$\text{Ar}\cdot + \text{Cu} \rightleftharpoons \text{Ar-Cu} \rightleftharpoons \text{Ar}^{-}\text{Cu}^{+}$$

[28] M. D. Rausch, *J. Org. Chem.*, 1961, **26**, 1802.
[29] W. A. Waters, "The Chemistry of Free Radicals," Clarendon Press, Oxford, 1948.
[30] W. S. Rapson and R. G. Shuttleworth, *Nature*, 1941, **147**, 675.
[31] H. E. Nursten, *J.*, 1955, 3081.
[32] M. Nilsson, *Acta Chem. Scand.*, 1958, **12**, 537; *Svensk. Kem. Tidskr.*, 1961, **73**, 9.
[33] J. Forrest, *J.*, 1960, (*a*) 566, (*b*) 574, (*c*) 581, (*d*) 589, (*e*) 592, (*f*) 594.
[34] J. S. Campbell and C. Kemball, *Trans. Faraday Soc.*, 1961, **57**, 809; 1963, **59**, 2583.

Within the broader area of halide–metal reactions, those of the alkali metals are the most extensively studied. Sodium alkyls and aryls are well-known as end products or intermediates, but the first step in the reaction is a single-electron transfer to give a radical, as was shown more than 30 years ago by Paneth's sodium-flame experiments[29] and recently by a trapped-radical technique[35] at liquid-nitrogen temperature, which was effective not only for alkyl halides but also for iodobenzene:

$$\mathrm{PhI} + \mathrm{Na} \rightarrow \mathrm{Ph}\cdot + \mathrm{Na}^{+} + \mathrm{I}^{-}$$

There has been no similar demonstration of radical production in reactions of copper with halides. Phenylcopper(I)[36] results from the reaction $\mathrm{PhMgBr} + \mathrm{CuI} \rightarrow \mathrm{CuPh} + \mathrm{MgBrI}$ and is reported to be spontaneously oxidised to biphenyl and copper oxide by air. Good yields of biphenyl or bi-1-naphthyl were obtained by heating the appropriate copper(I) aryls (made from lithium aryls) in toluene under nitrogen.[37] This decomposition may proceed through aryl radicals, $\mathrm{CuAr} \rightarrow \mathrm{Cu} + \mathrm{Ar}\cdot$, but if the solvent is not attacked these cannot have much freedom in the system. The reactivity of copper(I) aryls towards aryl halides needs investigation: the reaction with alkyl halides, $\mathrm{CuPh} + \mathrm{AlkBr} \rightarrow \mathrm{PhAlk} + \mathrm{CuBr}$, was reported[36] to be moderately successful with allyl bromide but unsuccessful with n-butyl bromide.

The temperature needed for Ullmann coupling reactions[1] is commonly around 200°, though, depending on the reactivity of the halide, it may be as low as 100° or as high as 300°. High-boiling and relatively inert solvents such as nitrobenzene have sometimes been employed as diluents, and dimethylformamide (b.p. 153°) has recently been recommended[38] for the more reactive halides such as iodonaphthalene, halides of the type $\mathrm{C_6H_4X{\cdot}Hal}$ ($\mathrm{X = NO_2, CO_2Me, Me}$),[38] and iodides of the type $o\text{-}\mathrm{C_6H_4I{\cdot}COR}$;[39] its value may be due, at least partly, to its capacity to dissolve copper(I) halide from the surface of the metal. Solvents however are not invariably beneficial, since, as described in Section (*e*), they may participate in halide reductions.

Comparisons of the reactivity of different aryl halides in Ullmann coupling are available only from yield data, and these are rather poorly reproducible. For example, yields quoted[31,33e,40,41] for the halides *o*-, *m*-, and $p\text{-}\mathrm{C_6H_4Hal{\cdot}NO_2}$ vary by up to 20—30% and do not always show the same order of reactivity among members of the series. With respect to the nature of the halogen, the general trend of halide reactivity is $\mathrm{ArI > ArBr > ArCl}$, though there may be a little difference between bromides or

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[35] J. E. Bennett and A. Thomas, *Nature*, 1962, **195**, 995; 6th Symposium on Free Radicals, Cambridge, 1963.

[36] H. Gilman and J. M. Straley, *Rec. Trav. chim.*, 1936, **55**, 821.

[37] R. G. R. Bacon and H. A. O. Hill, unpublished investigations.

[38] N. Kornblum and D. L. Kendall, *J. Amer. Chem. Soc.*, 1952, **74**, 5782.

[39] R. G. R. Bacon and W. S. Lindsay, *J.*, 1958, 1375, 1382.

[40] W. Davey and R. W. Latter, *J.*, 1948, 264.

[41] P. H. Gore and G. K. Hughes, *J.*, 1959, 1615.

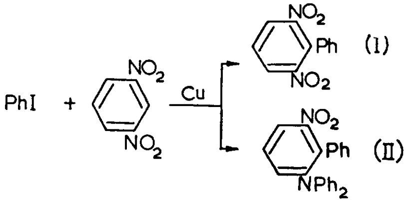
iodides of the more reactive types; coupling of aryl fluorides is unknown.

The strong activating effect of an electron-attracting group in an *ortho*-position has long been known; *e.g.*, potassium *o*-bromobenzoate underwent Ullmann coupling in water at 90—100°.[42] In a study of 26 substituted halogenobenzenes,[33e] Forrest observed that NO_2 or CO_2Me groups were strongly activating in the *ortho*-position but not in *meta*- or *para*-positions; this was also found with more weakly electron-attracting groups, such as CN; moderate activation occurred with the electron-donating OMe group, and also with CH_3 and Cl, and in all three cases these effects were similar in *ortho*-, *meta*-, and *para*-positions. Such observations illustrate the marked differences in substituent effects, which are generally observed between copper-promoted replacements of aryl halides, and, *e.g.*, their reactions with alkali-metal salts or other nucleophils; distinctive reaction mechanisms are thus indicated. It is conceivable that the particularly strong effect of some *ortho*-substituents may be due to their capacity to associate with the metal, and thus to facilitate reaction with neighbouring halogen, *i.e.*, there may be a resemblance to the "built-in solvation" effect, discussed by Bunnett[43] for other reactions of aryl halides with *ortho*-NO_2 or -CO_2R substituents.

Although in favourable cases the yields of symmetrical biaryls may attain 70—90% in Ullmann coupling, they are frequently much lower owing to incomplete reaction or to the formation of identifiable or resinous by-products. The most important side reaction is the substitutive reduction ArHal → ArH, discussion of which is deferred until Section (*e*). A second type of reaction is substitution between the halide and a suitable aromatic compound which may be present:

$$\mathrm{ArHal} + \mathrm{Ar'H} \rightarrow \mathrm{Ar\text{-}Ar'}$$

This result was attributed[30] to attack by aryl radicals in the case of iodobenzene and ethyl benzoate, which formed some ethyl 2- and 4-biphenylcarboxylate. More complicated substitutions have been observed[33a,b,c] between iodobenzene or substituted iodobenzene and *meta*-dinitro-compounds, which thereby became linked at the position between the nitro-groups, giving biaryls of types (I) and (II), here shown for the simplest members of the series, each being obtained in yields of up to 12%:



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[42] W. R. H. Hurtley, *J.*, 1929, 1870.
[43] J. F. Bunnett, *Quart. Rev.*, 1958, **12**, 1.

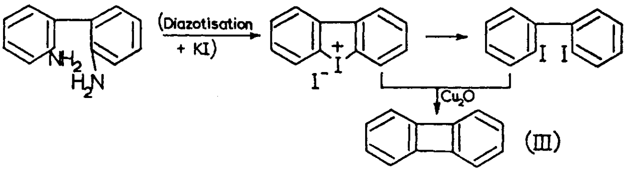
The compound (II) presumably results from copper-catalysed reduction of NO_2 to NH_2 by hydrogen from an organic donor, or hydrogen iodide, followed by catalysed arylation of the amino-function.

A third variety of side reaction may occur if more than one kind of halogen atom is present in the system. This is a halogen-transfer (see p. 120) between an aryl halide and a copper(I) halide produced in the coupling; nuclear bromine may thus be replaced by chlorine, nuclear iodine by bromine or chlorine. In one example the side-reaction $o\text{-}C_6H_4ClI \rightarrow o\text{-}C_6H_4Cl_2$ occurred[32] only to the extent of 5%, but replacement of iodine by bromine has been observed[33d] in yields of up to 50% from mixtures of substituted halides of the types C_6H_4XBr and C_6H_4YI. Fourthly, there may be side reactions such as copper-induced decarboxylation of CO_2H groups and condensation of a halide with compounds containing phenolic or amino-groups. More obscure in origin are the dibenzofurans which have been detected as by-products in reactions of *o*-chloroiodobenzene[32] and of 1-bromo-2-iodo-4,5-dimethoxybenzene,[45e] though they could be formed by internal condensation of halogenohydroxybiphenyls, water being the source of the phenolic group.

Copper(I) salts, produced in the Ullmann coupling, appear to be ineffective in the further reaction

$$2\text{ArHal} + 2\text{Cu}^{+} \rightarrow \text{Ar·Ar} + 2\text{Cu}^{2+} + 2\text{Hal}^{-}$$

There is a method of coupling salts of iodosulphonic acids, with aqueous copper sulphate and copper,[44] which could conceivably involve Cu^I species, but the chemistry of this system has not been investigated. With reactive types of aryl halides, coupling to the extent of 5—15% has lately been effected with cuprous oxide.[26] The most important application of this oxide as a coupling agent is in the preparation of biphenylenes. These difficultly accessible compounds are obtained, *e.g.* in 10—40% yield, by briefly heating *oo*′-di-iodobiaryls with a large excess of the oxide at about 350°. The final stages of a synthesis of the parent compound (III) are as follows:



(III)

This process has been developed by Baker, McOmie, and their co-workers,[45] and by Cava and his co-workers,[46] following an earlier investiga-

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[44] H. J. Barber and S. Smiles, *J.*, 1928, 1141; W. M. Cumming and G. D. Muir, *J. Roy. Tech. Coll. Glasgow*, 1937, **4**, 61.

[45] W. Baker, J. F. W. McOmie, *et al.*, *J.*, (*a*) 1954, 1476; (*b*) 1958, 2658; (*c*) 1961, 3986; (*d*) 1963, 922.

[46] M. P. Cava and J. F. Stucker, *J. Amer. Chem. Soc.*, 1955, **77**, 6022.

tion by Lothrop[47] who found copper metal to be ineffective. However, analogous cyclisations giving a biphenylene or triphenylene have been detected as side reactions between copper and certain *o*-dihalides,[32,48] and have been attributed to the polymerisation of benzyne intermediates.

The Ullmann coupling reaction is remarkably specific to compounds in which the halogen is attached to a benzenoid or aromatic-type heterocyclic nucleus, and appears to have little applicability to alkyl or monoarylalkyl halides. On the other hand, diarylalkyl halides are highly responsive. Recent investigations[26] show that the reaction $2Ph_2CHBr \rightarrow Ph_2CH{\cdot}CHPh_2$ is effected practically quantitatively with many metals, and particularly readily with copper or silver, and that it also succeeds with copper(I) compounds. Similarly, a diarylalkyl dihalide gives the olefinic coupled compound with copper, as in the reaction[49] $2Ph_2CCl_2 \rightarrow Ph_2C{:}CPh_2$.

(*c*) **Reductive Coupling of Organosulphur Compounds.**—The coupling of aromatic compounds containing bivalent sulphur functions has been less investigated than the coupling of halides, but it appears to proceed much less readily. The following four examples[50–53] show the reaction of copper with XS-substituted aryl compounds of suitable structure and also with aryl compounds containing α-thio-groups:

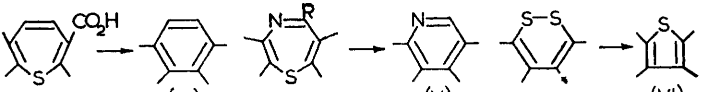
$ArS{\cdot}SAr$ or $Ar{\cdot}SCN \rightarrow Ar{\cdot}Ar$
(Ar = 1-anthraquinonyl)

$Ar{\cdot}SH \rightarrow Ar{\cdot}Ar(60\%) + ArH(25\%) + Cu_2S + H_2$
(Ar = 9-acridyl)

$(Ar{\cdot}CHS)_3 \rightarrow ArCH{:}CHAr\ (20\text{—}70\%)$
($Ar = C_6H_5, C_6H_4X, C_{10}H_7$ etc.)

$Ar_2CS \rightarrow Ar_2C{:}CAr_2\ (75\text{—}90\%)$
($Ar = C_6H_5, C_6H_4X$, etc.)

Closely related to these intermolecular reactions are the intramolecular ring-contractions which occur with extrusion of sulphur when certain polycyclic compounds are heated with copper, *e.g.*, in boiling quinoline or diethyl phthalate. The following examples (partial structures shown) from the papers of Loudon and his co-workers[54] show the formation of a phenanthrene (IV) and a phenanthridine derivative (V):



(IV) (V) (VI)

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[47] W. C. Lothrop, *J. Amer. Chem. Soc.*, 1941, **63**, 1187.
[48] E. R. Ward and B. D. Pearson, *J.*, 1961, 515.
[49] *Org. Synth.*, 1951, **31**, 104.
[50] E. Kopetschni, G. P. 360,419 and 362,984.
[51] K. Lehmstedt and H. Hundertmark, *Ber.*, 1930, **63**, 1229.
[52] J. H. Wood, J. A. Bacon, A. W. Meibohm, W. H. Throckmorton, and G. P. Turner, *J. Amer. Chem. Soc.*, 1941, **63**, 1334.
[53] A. Schönberg, O. Shütz, and S. Nickel, *Ber.*, 1928, **61**, 1375.
[54] I. D. Loudon *et al.*, *J.*, 1957, 3814, 3818; 1958, 1588; 1959, 885.

Partial extrusion of sulphur from a disulphide bridge[55] may give a thiophen derivative (VI):

Reaction of sulphur compounds in quite different circumstances is recorded[56] for the coupling process with sulphonyl chlorides

$$ArSO_2Cl + ArH \rightarrow Ar{\cdot}Ar' + SO_2 + HCl$$

which is effected by heating, and is regarded as homolytic in character; copper(I) salts are catalysts.

(*d*) **Reductive Coupling of Diazonium Salts.**—Diazonium salts are highly susceptible to Sandmeyer-type substitution reactions,[2] promoted by copper or copper(I) compounds in aqueous solution. Reductive coupling is also a copper-promoted reaction, but requires closely defined experimental conditions since it is subject to competition from substitution. It is further complicated by the possibility that the loss of nitrogen is either complete or partial, leading to a biaryl or an azo-compound respectively. The result, in summary, is that ArN_2^+ may give Ar·Ar, ArN:NAr, ArX, or ArH.

Observations on the coupling reactions[2,3] were first made in the 19th century. The preferred technique, originating with Vorländer and Meyer and developed by Atkinson and his co-workers,[57] consists in treating the diazonium salt solution, according to a prescribed mixing procedure, with a suitable copper reagent. The latter may consist of an equimolar quantity of freshly precipitated copper(I) oxide suspended in aqueous ammonia, or an aqueous solution, presumably containing $Cu(NH_3)_2^+$ ions, prepared by reducing a copper(II) salt in the presence of ammonia with hydroxylamine, sulphur dioxide, or a ferrous salt; an ammoniacal suspension of copper is an alternative reagent.[57] Little is known concerning reaction mechansims or changes occurring in the copper species. It is considered that the latter functions reductively; *i.e.*, the overall change is theoretically:

$$2ArN_2^+ + 2Cu^+ \rightarrow Ar{\cdot}Ar + 2Cu^{2+} + 2N_2$$

Known substituent effects are similar to those discussed for the coupling of halides, in the sense that an electron-attracting substituent, particularly in an *ortho*-position, favours biaryl production. The reaction has been most successful (40—90% yields) with diazotised *o*-amino-carboxylic acids of the benzene series,[57] and with corresponding *ortho*-[58] or 1,8-compounds[2] of the naphthalene series. An *o*-SO_3H group has led to a biaryl; *o*-, *m*-, or *p*-NO_2 gave mainly a biaryl, but also an azo-compound; with no substituents, or with substituent CH_3-, OH-, or NHAc-groups, only azo-compounds have been obtained.[57] By-products, ArCl, ArOH, ArOAr,

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[55] W. L. F. Armarego, *J.*, 1960, 433.

[56] P. J. Bain, E. J. Blackman, W. Cummings, S. A. Hughes, E. R. Lynch, E. B. McCall, and R. J. Roberts, *Proc. Chem. Soc.*, 1962, 186.

[57] E. R. Atkinson *et al.*, *J. Amer. Chem. Soc.*, 1940, **62**, 1704; 1941, **63**, 730; 1943, **65**, 476; 1945, **67**, 1513; 1950, **72**, 1397.

[58] R. G. R. Bacon and R. Bankhead, *J.*, 1963, 839.

$ArNH_2$, or Ar_2NH, may result from competitive substitutions. Unsymmetrical biaryls have been obtained from mixtures of diazotised *o*-aminocarboxylic acids,[57] and azo-linked polymers are preparable from tetrazo-compounds.[59]

A variation on biaryl formation is displayed when copper metal acts as an electron donor for both ArN_2^+ and Hg^{2+} in the addition compound of a diazonium chloride and mercury(II) chlorides;[60] this produces a mercury diaryl:

$$2ArN_2^+ + 2Hg^{2+} + 6Cu \rightarrow Ar{\cdot}Hg{\cdot}Ar + Hg + 2N_2 + 6Cu^+$$

(*e*) **Substitutive Reduction of Halides.**—Processes described in the literature for effecting reductions of the type ArHal → ArH usually involve metal hydrides, or various hydrogen donors in association with metal catalysts. Biaryl formation is sometimes a competing reaction. On the other hand, when the Ullmann coupling method is used to prepare biaryls, substitutive reduction is sometimes a side reaction; this is also the case in preparations of diaryl ethers or diarylamines by the Ullmann method (p. 122). Recent investigations have shown[26,61,62] that when hydrogen donors and experimental conditions are suitably chosen, copper-catalysed substitutive reduction of halides becomes a major reaction. For specific acceptors, hydrogen transfer is thus emerging as an important feature of copper chemistry. Aryl halides, and certain other types of halides constitute the main group of acceptors, but some sulphur compounds and diazonium salts are also responsive. Individual aryl halides differ very widely in their capacity for reduction, and this feature needs further investigation. When the response of acceptors to catalysed reduction is being assessed control experiments are necessary in view of the possibility of some degree of non-catalysed donor–acceptor interaction, which is not always predictable from the literature. A great variety of donors may be used; the following sub-sections deal with three types which have been investigated.

Carboxylic acids and their derivatives as donors. This was first exemplified[63] by the conversion of *ortho*-nitro-halides into the corresponding dehalogenated nitro-compounds, with copper as catalyst, in molten benzoic acid or in hexanoic acid at 150—200°; the carboxyl group was assumed to be the source of hydrogen. A later investigation[64] showed that a less reactive halide, such as bromonaphthalene, was reduced by a mixture of cuprous oxide, acetic anhydride, and pyridine; carboxylic hydrogen was again thought to be involved, but its source was not obvious. This process

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[59] A. A. Berlin, V. I. Liogonkii, and V. P. Parini, *J. Polymer Sci.*, 1961, **55**, 675.

[60] *E.g.*, *Org. Synth.*, Coll. Vol. II, 381.

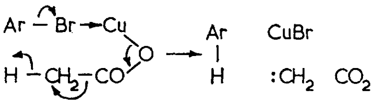
[61] R. G. R. Bacon, S. C. Rennison, and O. J. Stewart, *Proc. Chem. Soc.*, 1964, 409.

[62] R. G. R. Bacon and H. A. O. Hill, *J.*, 1964, 1112.

[63] W. T. Smith, *J. Amer. Chem. Soc.*, 1949, **71**, 2855; W. T. Smith and L. Campanaro, *ibid.*, 1953, **75**, 3602.

[64] W. G. H. Edwards and R. G. Stewart, *Chem. and Ind.*, 1952, 472; W. G. H. Edwards and G. K. McIndoe, *ibid.*, 1953, 1091.

has proved useful in a synthesis.[65] In a recent study,[62] 1-bromonaphthalene was converted into naphthalene in pyridine with copper(I) acetate, or with a reacting mixture of cuprous oxide with acetic acid, monofluoroacetic acid, acetic anhydride, or hexadeuteroacetic anhydride. Since, with the last-named reagent, about 70% of the product was deuteronaphthalene, the major source of the transferred hydrogen is clearly an α-carbon atom. Decarboxylation simultaneously occurs, and the process has tentatively been represented as involving transfer of hydride ion by a cyclic process within a halide–copper(I) salt complex; the carbene postulated as a decomposition product may be the precursor of the tars which are prominent in these reactions:

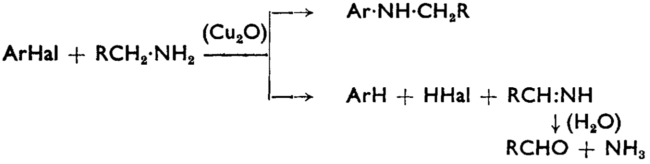


Formic acid undergoes catalysed decarboxylation at a low temperature, and is ineffective as a reductant, but formate ion has moderate activity as a donor[61] and can plausibly be considered to function by copper-catalysed hydride-ion transfer:

$$\mathrm{ArHal} + \mathrm{H{\cdot}CO_2^-} \rightarrow \mathrm{ArH} + \mathrm{Hal^-} + \mathrm{CO_2}$$

The observation[62] that benzoic anhydride also caused reduction suggests that aromatic nuclear hydrogen can be transferred to an acceptor. With *o*-chlorobenzoic anhydride or α-chlorinated acetic acid derivatives, bromonaphthalene was converted into chloronaphthalene. This suggests that chlorine may likewise be transferred, but the results are ambiguous because any copper(I) chloride produced by decomposition of these acid derivatives would cause the same substitution (p. 120).

Alcohols, amines, and alkoxides. An old patented process[66] for reducing picryl chloride to 1,3,5-trinitrobenzene included the use of copper and an aliphatic alcohol. This is an exceptional case, and recent experience[61] suggests that an easily dehydrogenated alcohol, such as diphenylmethanol, is needed for the reduction of moderately reactive halides such as 1-bromonaphthalene, and the yield, even so, is low. Amines appear to be a good deal more effective than alcohols,[67] and with cuprous oxide, *e.g.*, in boiling collidine, they effect reduction in competition with substitution, *e.g.*:



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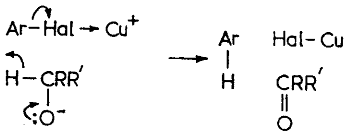
[65] R. D. Topsom and J. Vaughan, *J.*, 1957, 2842.
[66] J. Meyer, German P. 234,726.
[67] R. G. R. Bacon and O. J. Stewart, *J.*, 1965, in the press.

Alkoxides are much more effective than alcohols in catalysed hydrogen transfer. An example appeared[68] in an examination of the reaction system 1-$C_{10}H_7Br$–NaOMe–Cu_2O–H·CO·NMe_2(solvent) which produced both naphthalene and the expected 1-methoxynaphthalene. Further investigation[26,61] has shown reduction of aryl halides to be a general reaction of primary or secondary alkoxides, occurring, *e.g.*, in refluxing collidine or dimethylacetamide in the presence of cuprous oxide or copper. With alcohols or amines as donors, there is uncertainty concerning whether the reaction is homolytic or heterolytic, but reduction by an alkoxide can reasonably be represented as transfer of a hydride ion to the halide, which may be activated by association with the copper:



Proof of the transfer of α-hydrogen requires deuterium or tritium labelling, as has already been done[69] for the related uncatalysed reaction:

$$ArN_2^+ + CHRR'{\cdot}OH \rightarrow ArH + H^+ + CORR'$$

The observation[61] that t-butoxide ion is a reductant indicates that β-C–H bonds may also be utilised.

These results have prompted examination of copper(I) hydride as a reductant. It is an unstable compound[70] even at room temperature, and has proved ineffective with aryl halides,[62] probably because of loss of hydrogen before the temperature needed for reduction had been attained. Nevertheless, its existence suggests that interactions of the type

$$Cu^+ \; H^- \rightleftharpoons Cu\text{-}H \rightleftharpoons Cu \; H\cdot$$

are significant in copper-catalysed hydrogen transfer.

Aromatic compounds as donors. Observations reported from time to time that dehalogenated compounds are by-products of Ullmann coupling reactions, indicate that some of the aromatic halide molecules are acting as hydrogen donors for other halide molecules. For example, reduction has been found, to varying extents, with *o*-bromobenzoic acid,[42] *o*-iodocarbonyl compounds,[39] 1-iodo-2-methylnaphthalene, and methyl 1-bromo-2-naphthoate.[58] Reduction has also been observed when tetralin was used as solvent,[71] and when catechol or resorcinol were present[31] in Ullmann coupling reactions. Extensive reduction occurred in Ullmann-type

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[68] R. G. R. Bacon and H. A. O. Hill, *J.*, 1964, 1108.

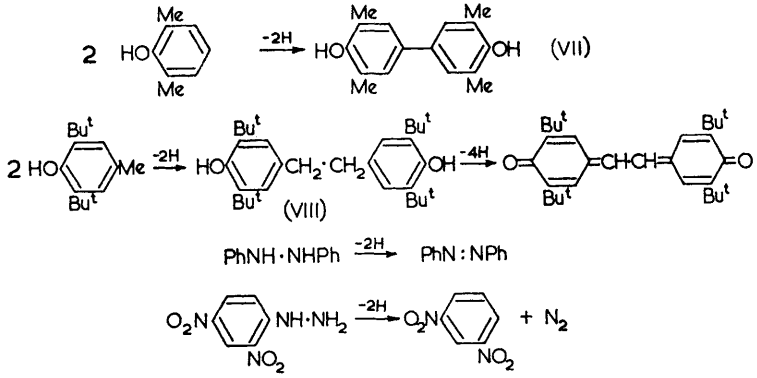
[69] L. Melander, *Arkiv Kemi*, 1951, **3**, 525; A. F. Rekasheva and G. P. Miklukhin, *Doklady Akad. Nauk S.S.S.R.*, 1951, **80**, 221; *Zhur. obshchei Khim.*, 1954, **24**, 96.

[70] E. Wiberg and W. Henle, *Z. Naturforsch.*, 1952, **76**, 250.

[71] R. W. Hardacre and A. G. Perkin, *J.*, 1929, 180; M. S. Lesslie and E. E. Turner, *J.*, 1932, 281.

preparations of complex diaryl ethers containing carboxyl groups,[72] and also when phenols containing nitro or carboxyl groups were used in reactions with aryl halides and cuprous oxide.[67] There are numerous cases of reduction occurring as a side reaction in Ullmann amination processes used in syntheses of acridones[73] (p. 123).

Recent investigations[26,61] reveal a widespread capacity of aromatic species to act as donors for halides, *e.g.*, in refluxing collidine or dimethylacetamide containing a suspension of cuprous oxide or copper. Depending on the activities of the donor and acceptor molecules, reduction may vary from less than 10% to more than 80%. Donors include phenols, quinones, amines, hydrazino-compounds, hydrazo-compounds, and nitro-compounds, and the source of hydrogen may be either the nucleus or a substituent group. This is illustrated by the following examples, in which the origin of the transferred hydrogen atoms is shown by the nature of the isolated dehydrogenated products; these are detected particularly readily when an active acceptor, such as *o*-bromonitrobenzene, is employed. The products (VII) and (VIII) are the result of the oxidative coupling of phenols, hydrogen having been lost from a *para*-nuclear position and a *para*-methyl group respectively; the other two cases show the loss of hydrogen from a hydrazo- or hydrazino-group.



These dehydrogenation products are identical with those obtained when the donors participate in oxidations, *e.g.*, by transition-metal ions, which are regarded as homolytic in character. Hence, it is possible that these copper-catalysed hydrogen transfers involve atoms rather than ions. Observed side reactions are production of the biaryl Ar·Ar, catalysed substitution of the halide by a nucleophilic donor, and catalysed oxidation of the donor if air is present. There are indications that molecules containing pyridine rings may also serve as donors; this may complicate their use

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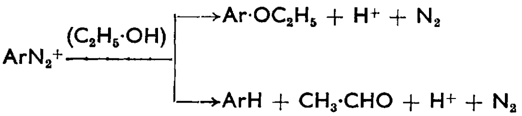
[72] (*a*) H. King, *J.*, 1939, 1157; (*b*) W. M. Whaley, L. Starker, and M. Meadow, *J. Org. Chem.*, 1953, **18**, 833.

[73] R. M. Acheson, "Acridines," Interscience Publishers, New York, 1956, p. 148.

as solvents.[26,74] Indeed, it appears that very numerous variations may be made in the nature of the reductant. In one example,[75] a redox reaction between a copper(II) salt and ascorbic acid or inorganic reductants resulted in conversion of *o*-iodobenzoic acid into benzoic acid.

(*f*) **Substitutive Reduction of Other Types of Aromatic Compounds.**—Apart from halides, diazonium salts provide the chief class of aromatic compounds for which copper species are known to catalyse substitutive reduction, $\mathrm{ArN_2^+} \rightarrow \mathrm{ArH}$. This is a much easier process than reduction of halides, and several methods for effecting it have been discussed in Reviews.[3,76] Alcohols, particularly ethanol, have a long history of application as reductants, but suffer from the important defect that the production of an ether is a competitive and often dominant reaction:



$$\mathrm{ArN_2^+} \xrightarrow{(\mathrm{C_2H_5{\cdot}OH})} \begin{cases} \mathrm{Ar{\cdot}OC_2H_5 + H^+ + N_2} \\ \mathrm{ArH + CH_3{\cdot}CHO + H^+ + N_2} \end{cases}$$

The best examples of reduction with ethanol generally involve diazonium salts containing nitro-, carboxylic, or halogeno-substituents. The reactions can be aided by copper species, and about 20% of the reductions by ethanol tabulated by Kornblum[76] were effected in the presence of copper powder, cuprous oxide, or copper sulphate. The most generally satisfactory reductant for diazonium salts is hypophosphorous acid.[77] Its reaction was found to be catalysed by several inorganic species, including copper metal and copper(II) salts; a free-radical chain mechanism was postulated.[77]

There is very little information about the copper-promoted reduction of nitrogen-containing compounds other than diazonium salts. Dissolution of cuprous oxide in concentrated sulphuric acid containing *p*-chloronitrobenzene gave a good yield of *p*-chloroaniline.[78] This method, which probably involves copper(I) sulphate, has also been used for the substitutive reduction of diazonium salts.[79] Little is known also concerning the response of sulphur-containing functional groups. When 2,6-dimethylphenol was examined as a hydrogen donor for 1-nitro-2-thiocyanatobenzene,[61] in conjunction with cuprous oxide (as for aryl halides), the following reactions were observed:

$$\mathrm{2Ar{\cdot}SCN} \rightarrow \mathrm{ArS{\cdot}SAr} \rightarrow \mathrm{ArSAr}$$

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[74] R. G. R. Bacon and H. A. O. Hill, *J.*, 1964, 1097.

[75] M. Anbar, S. Guttmann, and C. Friedman, *Proc. Chem. Soc.*, 1963, 10.

[76] N. Kornblum, *Org. Reactions*, 1944, **2**, 262.

[77] N. Kornblum and A. E. Kelly, *Science*, 1953, **117**, 379; N. Kornblum, G. D. Cooper, and J. E. Taylor, *J. Amer. Chem. Soc.*, 1950, **72**, 3013.

[78] G. C. Finger and R. H. White, *J. Org. Chem.*, 1958, **23**, 1612.

[79] H. H. Hodgson and H. S. Turner, *J.*, 1942, 748; H. H. Hodgson and S. Birtwell, *J.*, 1943, 433.

Oxidation processes

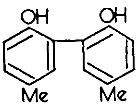
Oxidation of aromatic compounds can be effected by copper(II) compounds, occasionally by copper(III), and often by copper(I) or copper(II) acting in conjunction with various oxidants. As in other aromatic oxidation processes, the substrate may undergo dehydrogenation, dehydrogenative coupling, and various kinds of oxygenation, and a mixture of products often results. The classification of reactions used below is therefore somewhat arbitrary. The discussion does not include such side-chain reactions as the dehydrogenation of benzoin to benzil,[80] or the coupling of phenylacetylene to diphenyldiacetylene,[81] exemplifying characteristic effects of copper which are not confined to the aromatic series.

Biaryl- or Polyaryl-formation by Oxidative Coupling.—The following are coupling reactions of diverse type in which the use of copper compounds is a common feature.

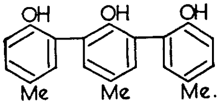
(*a*) Salts of copper(II) and of some other transition metals oxidise solutions of Grignard reagents, causing a coupling of the aryl group; biaryls may then be obtained in 80—90% yield.[82] This effect can plausibly be represented as a single-electron transfer to the aryl carbanion, followed by pairing of the resulting radicals:

$$\mathrm{Ph^{-}MgBr^{+} + Cu^{2+} \rightarrow Ph\cdot + MgBr^{+} + Cu^{+}; \quad 2Ph\cdot \rightarrow Ph\cdot Ph}$$

(*b*) When no other reagents are present, an aqueous copper(II) salt solution is an inadequate oxidant for the aromatic ring, even for compounds as reactive as phenols. Under more drastic conditions, *i.e.*, by employing a copper(II) salt in an excess of a molten phenol at 180—220°, smooth oxidation occurs[83] giving good yields of nuclear-linked dimers and trimers, provided that one or two of the reactive positions are blocked by alkyl groups. Thus *p*-cresol gave the dimer (IX) and the trimer (X), together with Pummerer's ketone. These are well-known effects of phenol oxidations by transition-metal ions, and occur through phenoxy-radicals.[84]



(IX)



(X)

(*c*) A special facility for displacement is found in a boronic acid group attached to a benzene ring. Oxidation by copper(II) acetate[85] gives a biaryl

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[80] *Org. Synth.*, Coll. Vol. I, 80.

[81] G. Eglinton and A. R. Galbraith, *J.*, 1959, 889.

[82] M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Constable and Co., London, 1954, ch. 5; E. Sakellarios and T. Kyrimis, *Ber.*, 1924, **57**, 322.

[83] W. W. Kaeding, *J. Org. Chem.*, 1963, **28**, 1063.

[84] W. A. Waters, "Mechanisms of Oxidation of Organic Compounds," Methuen and Co., London, 1963.

[85] Z. Holzbecher, *Chem. Listy*, 1952, **46**, 17.

by coupling, whilst phenol-formation, by oxygenation, is a competing process; the overall reactions are:

$$2\mathrm{Ar{\cdot}B(OH)_2} + 2\mathrm{Cu(OAc)_2} + 3\mathrm{H_2O} \rightarrow \mathrm{Ar{\cdot}Ar} + 4\mathrm{AcOH} + \mathrm{Cu_2O} + 2\mathrm{B(OH)_3}$$

$$\mathrm{Ar{\cdot}B(OH)_2} + 2\mathrm{Cu(OAc)_2} + 3\mathrm{H_2O} \rightarrow \mathrm{Ar{\cdot}OH} + 4\mathrm{AcOH} + \mathrm{Cu_2O} + \mathrm{B(OH)_3}$$

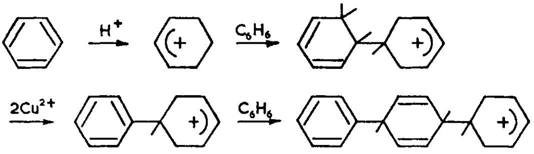
The following mechanism may be suggested:

$$\begin{tikzcd}
 & \mathrm{Ar{\cdot}Ar} \\
\mathrm{Ar{\cdot}B(OH)_2,H_2O} + \mathrm{Cu^{2+}} \arrow[r] & \mathrm{Ar\cdot} + \mathrm{B(OH)_3} + \mathrm{Cu^+} + \mathrm{H^+} \arrow[u, "\text{(coupling)}"'] \arrow[d, "(\mathrm{Cu^{2+}})"'] \\
 & \mathrm{Ar^+} + \mathrm{Cu^+} \arrow[d, "(\mathrm{H_2O})"'] \\
 & \mathrm{ArOH} + \mathrm{H^+}
\end{tikzcd}$$

Similar results are found[86] with ferroceneboronic acid.

(*d*) Progressive nuclear coupling, probably giving larger polymers than trimers such as (X), can be achieved[87] by treating benzene with the mixed reagent $\mathrm{AlCl_3{-}H_2O{-}CuCl_2}$, in which the Lewis acid is believed to cause cationic additive polymerisation, and the copper(II) causes dehydrogenation, giving a *para*-polyphenyl:

$$\mathrm{AlCl_3} + \mathrm{H_2O} \rightarrow \mathrm{AlCl_3(OH)^-\ H^+}$$



(followed by similar steps and terminated by loss of H⁺)

In connection with this reaction, the existence of the complex[10] $\mathrm{C_6H_6,AlCl_3,CuCl}$, is of interest.

(*e*) Another method of polymerisation[88] involves treatment of a 2,6-disubstituted phenol with a mixture of oxygen and copper(I) chloride in a heterocyclic base such as pyridine. This process yields polyethers by

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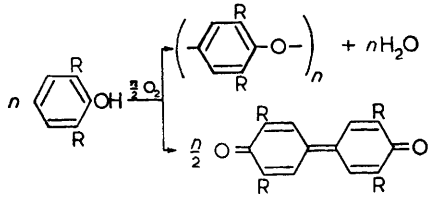
[86] A. N. Nesmeyanov, V. A. Sazonova, and V. N. Drozd, *Doklady Akad. Nauk. S.S.S.R.*, 1959, **126**, 1004.

[87] P. Kovacic and A. Kyriakis, *J. Amer. Chem. Soc.*, 1963, **85**, 454; P. Kovacic and J. Oziomek, *J. Org. Chem.*, 1964, **29**, 100.

[88] A. S. Hay, *J. Polymer Sci.*, 1962, **58**, 581; G. F. Endres and J. Kwiatek, *ibid.*, p. 593; G. F. Endres, A. S. Hay, and J. W. Eustance, *J. Org. Chem.*, 1963, **28**, 1300.

C–O coupling, in competition with formation of the dimeric diphenoquinone by C–C coupling:



C–O coupling is favoured by high base:copper ratios, by lower temperatures, and by avoidance of sterically hindered bases. It was considered that equilibria in the co-ordination of solvent ligands on a Cu^{II}–oxidant species determine these differences in catalyst behaviour:

$$\begin{tikzcd}
Cu^{II}L_n + L \arrow[r, shift left] \arrow[d, "(ArOH)"'] & Cu^{II}L_{n+1} \arrow[l, shift left] \arrow[d, "(ArOH)"] \\
\text{C—C-linked product} & \text{C—O-linked product}
\end{tikzcd}$$

An investigation[89] of related reactions has suggested that copper-oxygen interaction involves electron-transfer processes such as:

$$2Cu^+ + 2nL + O_2 \rightarrow (L_nCu^{2+})_2O_2^{2-} \rightarrow 2L_nCu^{2+}O^-$$

Such species presumably convert the phenol into phenoxy-radicals, which lead to C–C- or C–O-linked products, as has been discussed elsewhere.[84]

Dehydrogenation Processes.—The following examples illustrate the oxidative action of copper species, causing the loss of different kinds of labile hydrogen.

(*a*) Dehydrogenation of a hydroaromatic to an aromatic ring occurred in the case of 9,10-dihydroanthracene,[90] which gave anthracene with copper(II) chloride or bromide in boiling benzene (cf. p. 119). Under the same conditions, toluene underwent dehydrogenative coupling to bibenzyl.

(*b*) A substituent hydrazino-group undergoes the following degradation, through a presumed di-imide type of intermediate, when treated with hot aqueous copper sulphate:

$$\begin{tikzcd}
ArNH\cdot NH_2 \arrow[r, "2Cu^{2+}"] & ArN{:}NH + 2Cu^+ + 2H^+ \arrow[d] \\
& ArH + N_2
\end{tikzcd}$$

Thus the overall effect, if the hydrazine derivative is derived, as is commonly the case, from a reactive halide or diazonium salt, is to cause substitutive reduction of the starting material. This process began to be used in the

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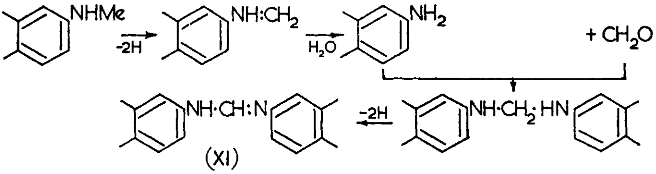
[89] E. Ochiai, *Tetrahedron*, 1964, **20**, 1831.
[90] D. C. Nonhebel, *J.*, 1963, 1216.

19th century[76] and there are numerous recent examples in aromatic and heterocyclic chemistry which demonstrate its utility. The results of a study[91] of the oxidation of phenylhydrazine by silver or mercuric oxide suggested that the di-imide intermediate breaks down to aryl radicals.

(*c*) Bradley's studies of indanthrone chemistry[92] provide several examples of effects of copper and its compounds in catalysing substitutions, and substitutive reduction, and in causing dehydrogenation of methylamino-groups. These oxidations were effected, *e.g.*, with copper or copper(II) acetate in boiling nitrobenzene, and led to demethylation, and to production of formaldehyde and of a formamidine derivative (XI) which was obtained as a copper(I) complex. The sequence of reactions is suggested in the following simplified scheme:

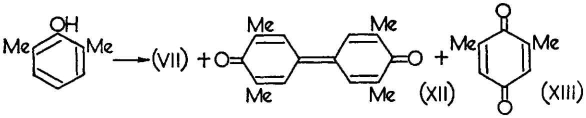


(*d*) A complicated reaction has been described for cyanide synthesis,[93] which in essence appears to involve the dehydrogenation of an intermediate imine. An aldehyde, *e.g.*, benzaldehyde, mixed with ammonia in methanol solution, is treated with oxygen in the presence of copper(II) chloride. The following reaction scheme, in which an imine radical is an intermediate, was suggested:

$$\begin{array}{rl}
 & \mathrm{PhCHO} + \mathrm{NH_3} \rightleftharpoons \mathrm{PhCH{:}NH} + \mathrm{H_2O} \\
 & \qquad\qquad\qquad\quad \downarrow (\mathrm{Cu^{2+}}) \\
\mathrm{PhC{:}N} + \mathrm{PhCH{:}NH} \xleftarrow{\text{(Disproportionation)}} & \mathrm{PhCH{:}N\cdot} + \mathrm{Cu^+} + \mathrm{H^+} \\
 & \quad \downarrow (\mathrm{O_2}) \\
 & \mathrm{PhC{:}N} + \mathrm{HO_2\cdot} \xrightarrow{(\mathrm{Cu^+})} \mathrm{HO_2^-} + \mathrm{Cu^{2+}}
\end{array}$$

Oxygenation Processes.—These are illustrated by reactions occurring (*a*) in aqueous copper-salt solutions and (*b*) in the thermal decomposition of copper salts of carboxylic acids.

(*a*) A typical result of an oxidation effected by transition-metal ions in aqueous solution is the conversion of 2,6-dimethylphenol into a mixture of the coupled product (VII), the corresponding diphenoquinone (XII), and the quinone (XIII):



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[91] R. L. Hardie and R. H. Thompson, *J.*, 1957, 2512.
[92] W. Bradley, *J.*, 1951, 2129, 2147, 2158, 2163, 2170, 2177.
[93] W. Brackman and P. J. Smit, *Rec. Trav. chim.*, 1963, **82**, 757.

The product (XII) is the result of further dehydrogenation of (VII), formed by dehydrogenative coupling of the phenol, and the quinone (XIII) is presumably a similar secondary oxidation product, formed from 2,6-dimethylhydroquinone, which has arisen by *para*-hydroxylation of the phenol. Hydroxylation of an aromatic nucleus by an aqueous solution of suitable transition-metal ions, M^{n+}, can be accounted for by a reaction sequence such as:

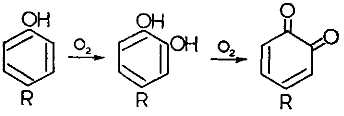
$$\begin{aligned}&ArH + M^{n+} \rightarrow Ar\cdot + M^{(n-1)+} + H^+\\&Ar\cdot + M^{n+} \rightarrow Ar^+ + M^{(n-1)+}\\&Ar^+ + H_2O \rightarrow ArOH + H^+\end{aligned}$$

Aqueous copper sulphate is without action on 2,6-dimethylphenol, but the products (XII) and (XIII) result if other oxidants, such as sodium persulphate, sodium hypochlorite, hydrogen peroxide, or oxygen, are also present.[94] It is known[95] in the case of persulphate and hypochlorite at least, that these oxidants convert Cu^{II} into Cu^{III}, since tervalent copper complexes with the formulae $Na_7Cu(IO_6)_2,16H_2O$ and $Na_9Cu(TeO_6)_2, 20H_2O$ are precipitated if the reaction is performed in the presence of sodium periodate or sodium tellurate respectively. In the absence of such complexing agents, reactive Cu^{3+} ions probably effect hydroxylation of 2,6-dimethylphenol as suggested above for the generalised case of transition-metal ions M^n; they could arise, *e.g.*, by the electron-transfer process

$$Cu^{2+} + S_2O_8^{2-} \rightarrow Cu^{3+} + SO_4\cdot^{-} + SO_4^{2-}$$

Copper(III) is greatly stabilised by periodate ligands and the isolated complex is less active than mixtures of copper(II) salts and appropriate oxidants; however, it converts 2,6-dimethylphenol into the diphenoquinone (XII)[94] and has been used as an analytical reagent for dihydric phenols.[96]

Oxidation of phenols by Cu^{II}–O_2 systems are of interest in connection with biological oxidations of the following type[97] effected by copper-containing oxidases:



Brackman and Havinga[98] have demonstrated similar effects in the laboratory by stirring methanolic solutions, containing copper(II) acetate, a monohydric or dihydric phenol, and a primary or secondary amine, such

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[94] R. G. R. Bacon and Alia Izzat, unpublished investigations.

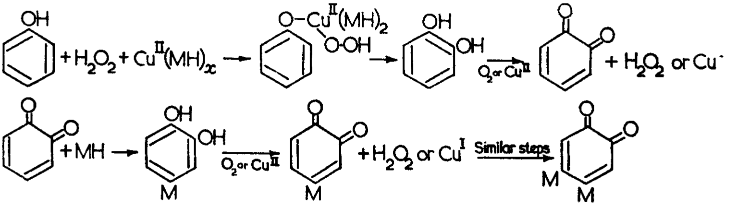
[95] L. Malatesta, *Gazzetta*, 1941, **71**, 467, 580; M. W. Lister, *Canad. J. Chem.*, 1953, **31**, 638.

[96] G. Beck, *Mikrochemie*, 1951, **38**, 152; cf. D. A. Keyworth and K. G. Stone, *Analyt. Chem.*, 1955, **27**, 833.

[97] *E.g.*, J. M. Nelson and C. R. Dawson, *Adv. Enzymology*, 1946, **4**, 99; A. B. Lerner, *ibid.*, 1953, **14**, 73.

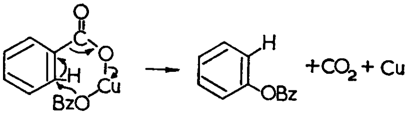
[98] W. Brackman and E. Havinga, *Rec. Trav. chim.*, 1955, **74**, 937, 1021, 1070, 1100, 1107.

as morpholine, in an oxygen atmosphere. Phenol was thus converted into *ortho*-benzoquinone, which then reacted further with the base and oxidant. Details of the Cu^{II}–O_2 interaction are uncertain (cf. p. 115), but hydrogen peroxide is involved in the suggested reaction sequence, which is briefly summarised in the following scheme. Here MH represents morpholine; one of its functions is to provide ligands in reversible association with copper ions.



In the case of similar experiments with naphthols, nuclear coupling competed with the oxygenation sequence. The same method of oxidation has been applied to aromatic amines.[99]

(*b*) Old observations on the effect of heat on copper salts of aromatic acids have recently been extended in industrial laboratories, resulting in a process which, in overall effect, converts the acid into a phenol.[100,101] The acid reacts with an inorganic copper(II) salt, or with copper(II) oxide, at 200—300°, the solvent being water or excess of the acid. Carbon dioxide is lost and an ester remains from which the phenol is obtained by hydrolysis. Alternative mechanistic possibilities have been discussed,[101] but it is agreed that a cyclic bond-breaking process is involved and that the copper(II) acts oxidatively, as in the following representation of the conversion of copper(II) benzoate into phenyl benzoate and thence into phenol:



The hydroxyl group enters the *ortho*-position to the lost carboxyl group; thus *o*-toluic acid gives *m*-cresol, whilst *m*-toluic acid gives *o*- and *p*-cresol. The overall effect on the inorganic material may be to produce a copper(I) salt, by the reaction Cu + Cu^{II} → $2Cu^{I}$. A variation on the process[102] consists in heating basic copper(II) benzoate, *e.g.*, in nitrobenzene at 200°,

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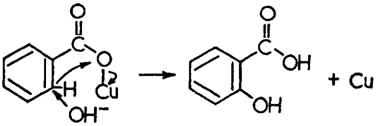
[99] G. Engelsma and E. Havinga, *Tetrahedron*, 1958, **2**, 289.

[100] W. W. Kaeding, *J. Org. Chem.*, 1961, **26**, 3144; W. W. Kaeding, R. O. Lindblom, and R. G. Temple, *Ind. Eng. Chem.*, 1961, **53**, 805.

[101] W. G. Toland, *J. Amer. Chem. Soc.*, 1961, **83**, 2507.

[102] W. W. Kaeding and A. T. Shulgin, *J. Org. Chem.*, 1962, **27**, 3551.

whereby hydroxylation occurs without loss of carbon dioxide, giving salicylic acid:



Halogenation by Copper(II) Chloride or Bromide.—Chlorination or bromination by copper(II) halides has some affinity with other reactions discussed in this Section, since a reduction of the inorganic halide occurs:

$$\mathrm{ArH + 2CuHal_2 \rightarrow ArHal + HHal + 2CuHal}$$

Unlike copper(II) iodide, the bromide and chloride dissociate to the copper(I) halide and halogen only at high temperatures.[103] In solution however, they serve as halogenating agents for phenols under mild conditions,[104] and for aromatic hydrocarbons under more drastic conditions.[90,105] Complicating features have been noted; *e.g.*, addition of copper(I) bromide removes an induction period, and the presence of traces of water causes halogenation to occur in the side chains of alkylbenzenes instead of in the nucleus. The process is clearly complicated, and factors contributing to it may be: dissociation of the halide in the solvent, $\mathrm{2CuBr_2 \rightleftharpoons 2CuBr + Br_2}$; heterolytic or homolytic substitution by the halogen, with catalysis by copper salts; complex-formation between the aromatic nucleus and the copper(I) halide; and the production of intermediate radicals and ions by electron-transfer processes

$$\mathrm{ArH + Cu^{2+} \rightarrow Ar\cdot + H^+ + Cu^+}$$

and

$$\mathrm{Ar\cdot + Cu^{2+} \rightarrow Ar^+ + Cu^+}$$

Substitution processes

Substitution Reactions of Aryl Halides.—Applications of copper are of two kinds: (*a*) Exchange reactions of the type ArHal + CuX → ArX + CuHal occur between the halide and a copper(I) salt, in which the ion X may be halide, cyanide, thiocyanate, or organic species such as SAlk, SAr, or C:CAr. (*b*) Copper, cuprous oxide, or other copper compound catalyses reactions of an aryl halide with a nucleophil, *i.e.*, ArHal + X^-(or HX) → ArX + Hal^- (or HHal). In processes of type (*b*), alkali-metal alkoxides, phenoxides, halides, cyanide, or other salts may provide the anion X^-, whilst amines and phenols are the main examples of non-ionic nucleophils, HX. These are generally heterogeneous processes,

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[103] S. A. Shchukarev and M. A. Oranskaya, *J. Gen. Chem. U.S.S.R.*, 1954, **24**, 1889; P. Barret and N. Guenebaut-Thevenot, *Bull. Soc. Chim. France*, 1957, 409.

[104] A. W. Fort, *J. Org. Chem.*, 1961, **26**, 765; E. M. Kosower, W. J. Cole, G.-S. Wu, D. E. Cardy, and G. Meisters, *J. Org. Chem.*, 1963, **28**, 630.

[105] J. C. Ware and E. E. Borchart, *J. Org. Chem.*, 1961, **26**, 2263, 2267.

though the catalyst commonly goes into solution, as reaction proceeds, when HX is the nucleophil. It may be supposed that catalysis involves the joint association of the aryl halide and the nucleophil with the surface of the cuprous oxide or other species employed.

Halide exchange. This has been noted as a side reaction in Ullmann coupling processes.[32,33a] It was used preparatively[106] for obtaining chloro-derivatives of polycyclic quinones from the corresponding bromo-compounds; reaction with copper(I) chloride was carried out in α-picoline. A study[74] of the reaction $1\text{-}C_{10}H_7Br + CuCl \rightarrow 1\text{-}C_{10}H_7Cl + CuBr$ showed it to occur rapidly and nearly quantitatively in suitable organic solvents at temperatures of the order of 110—150°. It was a second-order reaction and the rate was solvent-dependent, 10^5k at 110° being 0—2 for the heterocyclic bases or benzonitrile, 10 for dimethylacetamide, 12 for dimethylformamide, and 25 for dimethyl sulphoxide. It occurred only with copper salts. It was inhibited by chloride ion, by pyridine, and more strongly by 2,2′-bipyridyl. It was reversible, but with the equilibrium well in favour of formation of aryl chloride. The aryl fluoride did not react, and the ease of displacement of the other halogens was ArI > ArBr > ArCl, whilst the order of entry of halide from the salt was CuCl > CuBr > CuI. When applied to substituted bromobenzenes, $X{\cdot}C_6H_4Br$, the reaction with copper(I) chloride was remarkably insensitive to the substituent X. The *p*-methoxy- and *o*- or *p*-methyl-derivatives reacted at about the same rate as the unsubstituted bromide; the rates with the *m*- and *p*-nitro-compounds were respectively only 3 or 5 times as great, but a nitro-group in the *ortho*-position had the substantial effect of increasing the rate about 400-fold. These results are in marked contrast to those from substitutions not involving copper catalysis, which may show rates increased by 10^6 or more when nitro-substituents are present; they often show however similar enhancement of activity by *ortho*-nitro-[43] as compared with *para*-nitro-groups (cf. p. 104).

Discussion of the mechanism is handicapped by lack of information concerning the nature of the solute species in organic solutions of copper(I) salts. It may be supposed that dissolved copper(I) chloride is essentially monomeric and that un-ionised CuCl is associated with up to three solvent-molecule ligands in tetrahedral co-ordination; solvated ions, $Cu^+L_xCl^-$, may also be present in equilibrium with other species. The preference of copper(I) for polarisable ligands suggests the formation of a complex $ArHal \rightarrow CuClL_x$ preceding the substitution reaction. Similar intermediates, the formation constants of which should increase in the order ArCl, ArBr, ArI have been suggested elsewhere for CuX–aryl halide interactions[4,107] and for copper-catalysed reactions of amines and aryl halides.[73]

As in the analogous case of the Sandmeyer reaction,[2] views may vary concerning representations of the transition state in the exchange process. Possibilities are: a four-centre concerted process (XIV) without definable

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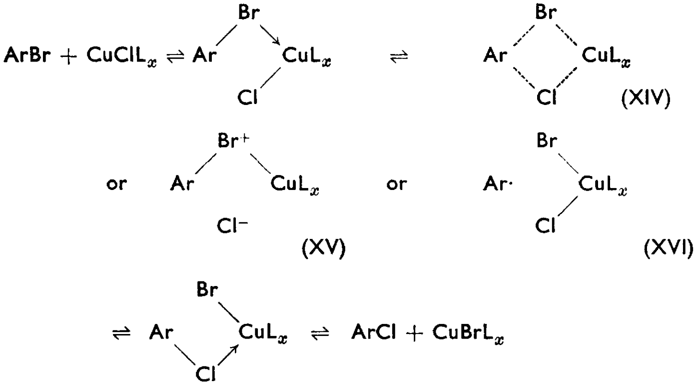
[106] W. B. Hardy and R. B. Fortenbaugh, *J. Amer. Chem. Soc.*, 1958, **80**, 1716.
[107] C. F. Koelsch and A. G. Whitney, *J. Org. Chem.*, 1941, **6**, 795.

intermediates; an intermediate ionisation step (XV) (alternatively, the copper halide may already be ionised) followed by nucleophilic displacement; and intermediate radical formation (XVI), with the metal alternating between the Cu^{I} and Cu^{II} state.



An objection to the intermediate-radical view is that, in a reaction with an aryl iodide, formation of an iodine-containing bivalent copper species, CuIHal, is unlikely. The ionic mechanism is attractive in that a positive charge on a substituent is known to increase its lability to nucleophilic attack.[108] The observed effects of inhibitions and, in part at least, effects due to solvent molecules, are attributed to their competing with the halide ligands for the copper(I) salt. An alternative method of effecting halogen exchange[68] is to treat the aryl halide with an alkali-metal halide or tetra-alkylammonium halide in, *e.g.*, boiling dimethylformamide containing a suspension of cuprous oxide; the observed order of halogen reactivity is the same as that noted above.

Cyanide formation. The use of copper(I) cyanide in substitutions of the type ArHal + CuCN → ArCN + CuHal is a well-established method of preparing aryl and other cyanides;[109] early studies of the process were made by Rosenmund and by von Braun. Traditionally, a mixture of the reagents is heated, either without solvent or in a heterocyclic base, but the method has recently been improved by the use of dimethylformamide or *N*-methylpyrrolidone as solvents.[110] Likewise 1-cyanonaphthalene was quantitatively obtained[74] from 1-bromonaphthalene in dimethyl sulphoxide, in 2 hours at 180°, as compared[111] with a 90% yield being obtained in quinoline in 15 hours at 215°. The reaction with bromonaphthalene

[108] B. A. Bolto and J. Miller, *Austral. J. Chem.*, 1956, **9**, 74.

[109] P. Kurtz, in Houben-Weyl, "Methoden der Organischen Chemie," 4th edn., 1952, vol. 8, Part III, p. 302; D. T. Mowry, *Chem. Rev.*, 1948, **42**, 189.

[110] M. S. Newman and D. K. Phillips, *J. Amer. Chem. Soc.*, 1959, **81**, 3667; M. S. Newman and H. Boden, *J. Org. Chem.*, 1961, **26**, 2525; L. Friedman and H. Boden, *ibid.*, p. 2522.

[111] *Org. Synth.*, Coll. Vol. III, 631.

was slower than the corresponding reaction of the bromo-compound with copper(I) halides. This is in harmony with what has been stated concerning the halide-exchange reactions, since the stability constants of copper(I) complexes with cyanide are higher than those with the halides.

Formation of diaryl ethers. Ullmann and his co-workers[112] found that the reaction ArHal + KOAr′ → ArOAr′ + KHal was catalysed by copper, and they described numerous examples of the process; the halide, phenol, potassium hydroxide, and copper (~0·02 g.-atom per mole) were heated at ~200°. The more recent literature[113] reports yields of 55—65% with unsubstituted, or methyl- or methoxy-substituted reagents, and higher yields, at lower temperatures, when the halide is activated by a nitro-group. The method has given poor results[72] when applied to the synthesis of more complex, naturally occurring diaryl ethers containing carboxyl groups. In one such investigation[72a] improvements were made by using copper in the proportion of ~1 g.-atom per mole; cuprous oxide also proved effective. Another variation,[114] used for a kinetic investigation, consisted in using a small amount of a copper(II) halide with the aryl halide, phenol, and potassium hydroxide in diethylene glycol dimethyl ether as solvent; the effective catalyst was considered to be copper(I).

In a general investigation[68] of cuprous oxide as a catalyst for nucleophilic substitutions of aryl halides, this method was found to be effective with either phenol or sodium phenoxide; a suspension of the oxide (1—2 mol.) in boiling collidine or dimethylformamide was used. This process has found application in studies of alkaloid synthesis.[115] An evaluation of the method[67] has shown its utility with a wide range of halides and phenols, except when the latter are substituted by nitro- or carboxyl groups; under suitable conditions it gives better yields than the traditional Ullmann method. Copper, copper(I) oxide, and copper(II) oxide catalyse the reaction and, when phenols are used, the catalyst goes into solution as reaction proceeds, producing inactive copper halides. Reaction occurs more easily with sodium phenoxides than with phenols. There is a large solvent effect, which is not related to the basicity of the solvent. Substitutive reduction is an important side reaction and decarboxylation also occurs. An example of reduction[67] was the partial conversion of *o*-bromonitrobenzene into nitrobenzene by *p*-cresol, which thus gave the coupled dimer (IX) (p. 113), isolated as its di-*o*-nitrophenyl ether, formed by catalysed reaction with the aryl halide.

Amination processes. There are only occasional examples in the literature[116] of copper-catalysed substitution of the type shown on p. 109,

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[112] F. Ullmann and P. Sponagel, *Ber.*, 1905, **38**, 2211; F. Ullmann and A. Stein, *Ber.*, 1906, **39**, 622; *Annalen*, 1906, **350**, 83.

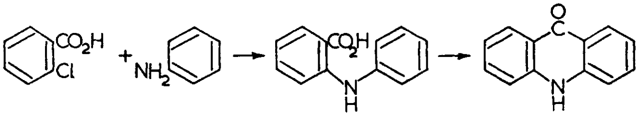
[113] *Org. Synth.*, Coll. Vol. II, 445, Coll. Vol. III, 566; P. A. Sartoretto and F. J. Sowa, *J. Amer. Chem. Soc.*, 1937, **59**, 603.

[114] H. Weingarten, *J. Org. Chem.*, 1964, **29**, 977, 3624.

[115] J. R. Crowder, E. E. Glover, M. F. Grundon, and H. X. Kaempfen, *J.*, 1963, 4578.

[116] *E.g.*, J. M. McManus and R. Herbst, *J. Org. Chem.*, 1959, **24**, 1042.

in which the nucleophil is an aliphatic amine. The best-known applications are industrial, as in the preparation of *N*-methylaniline from chlorobenzene, for which copper(I) chloride is the best of various catalysts examined.[117] More important in the laboratory are the applications arising from Ullmann's discovery[118] that small amounts of copper catalyse the condensation of aniline with *o*-chlorobenzoic acid, giving diphenylamine-2-carboxylic acid, from which acridone can be prepared:



The process is carried out in the presence of a base, usually potassium carbonate, and can alternatively be applied to mixtures of *o*-aminocarboxylic acids and aryl halides. This provides a standard route to acridine compounds and has been reviewed in detail by Acheson;[73] side reactions are reduction or coupling of the halide, and tar formation. Analogous processes have been developed for the synthesis of phenothiazines and phenoxazines.[119] Copper-catalysed condensation of an aryl halide with an *N*-acetylarylamine is known, but has been little investigated; oxygen may be involved at some stage in this reaction.[120]

Other substitutions of halides. Apart from the Ullmann-type preparation of diaryl ethers, other examples of substitution by oxygen-containing groups have occasionally been reported. Acetate ion, for example, reacts with *o*-halogenobenzoic acids in the presence of copper[42,121] giving, after hydrolysis, salicylic acid. The use of sodium alkoxides[68] and copper catalysts to introduce alkoxy-groups is limited by the marked tendency of reduction to occur (p. 109). It is relevant to refer here also to observations of catalysis by copper salts in decompositions of iodonium salts, such as

$$Ar_2I^+ + H_2O \rightarrow ArOH + ArI + H^+$$

which have been extensively studied. One of the mechanisms discussed for this catalysis[122] involves an oxidation–reduction cycle in the copper ion, somewhat similar to that shown in (XVI).

As would be expected from the strong bonding of sulphur-containing ions to copper, the exchange reactions of copper(I) thiocyanate or thiophenoxide with bromonaphthalene in organic solvents are slower than those of copper(I) halides.[74] Good yields of organic sulphides have been

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[117] E. C. Hughes, F. Veatch, and V. Elersich, *Ind. Eng. Chem.*, 1950, **42**, 787.

[118] F. Ullmann, *Ber.*, 1903, **36**, 2382.

[119] H. Gilman *et al.*, *J. Amer. Chem. Soc.*, 1944, **66**, 888; *J. Org. Chem.*, 1958, **23**, 1903; A. J. Saggiomo, P. N. Craig, and M. Gordon, *ibid.*, p. 1906; G. E. Bonvicino, L. H. Yogodzinshi, and R. A. Hardy, *ibid.*, 1961, **26**, 2793.

[120] P. E. Weston and H. Atkins, *J. Amer. Chem. Soc.*, 1928, **50**, 859.

[121] K. W. Rosenmund and H. Harms, *Ber.*, 1920, **53**, 2226.

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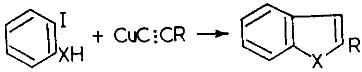
obtained however, *e.g.*, at 200° in quinoline, by reaction of aryl halides with copper(I) salts of alkane- or arene-thiols,[123] or by reaction of the halides with sodium salts of thiols in dimethylformamide in the presence of cuprous oxide.[74] Another variation in procedure involves the generation of copper(I) salts by the reaction $RS{\cdot}SR + 2Cu \rightarrow 2RSCu$ in dimethylacetamide in the presence of the aryl halide.[124]

The copper-catalysed formation of C–C bonds was exemplified, again in the case of the very reactive halide, *o*-bromobenzoic acid,[42] by its condensation with sodium derivatives of β-dicarbonyl compounds in the presence of copper bronze. Acetylene derivatives in good yield have recently been prepared in refluxing pyridine[125] by the reaction

$$ArI + CuC{:}CPh \rightarrow ArC{:}CPh$$

When reactive *ortho*-substituents, such as CO_2H, OH, or NH_2, are present in the halide, cyclisation with the acetylenic bond also occurs, giving isocoumarin, benzofuran, or indole derivatives respectively:



Other Copper-catalysed Substitutions.—In view of limitations of space and of the existence of an earlier Review,[2] the Sandmeyer and related substitution reactions of diazonium salts will not be discussed. Since that Review was written, neither practical nor theoretical aspects of the reaction have greatly altered. It resembles halide-replacement reactions by involving solutions of complexes of copper(I) with the reacting species. Similarly, different views may be held concerning mechanisms of decomposition of these complexes. The observation[126] of polymerisation of a vinyl monomer initiated by aryl radicals from the reaction lends support to the view that it may occur homolytically. Reference must also be made to a recent detailed Review[127] of the Meerwein reaction, in which an aryl group from decomposition of a diazonium salt adds to olefinic compounds. The reaction is copper-catalysed, is closely related to the Sandmeyer reaction, and has likewise been interpreted by both homolytic and heterolytic mechanisms.

Also available are accounts of two well-established processes in which copper catalysis is observed in replacement of nuclear hydrogen, with formation of a C–C linkage; the result is carbonylation in the Gatterman–Koch reaction[128] and cyclisation in the Pschorr reaction.[129]

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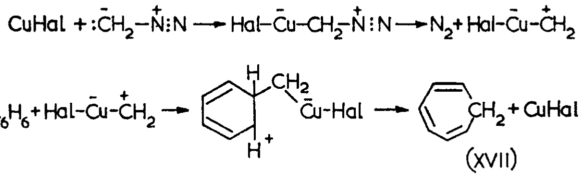
Ring enlargement

Copper and its salts catalyse the decomposition of diazomethane to carbene, which readily polymerises to polymethylene:

$$CH_2N_2 \rightarrow :CH_2 + N_2\ ;\quad n{:}CH_2 \rightarrow (CH_2)_n$$

In the presence of an olefin the carbene is largely consumed by addition to the double bond, giving a cyclopropane derivative. A similar addition reaction occurs with benzene, but is accompanied by ring opening, the product being cycloheptatriene (XVII). This method of preparation was independently discovered in three laboratories[130,131,132] and has been represented[130] as involving the following sequence, in which a copper complex is an intermediate.



$$CuHal + :\overset{-}{C}H_2-\overset{+}{N}{:}N \rightarrow Hal-\overset{-}{C}u-CH_2-\overset{+}{N}{:}N \rightarrow N_2 + Hal-\overset{-}{C}u-\overset{+}{C}H_2$$

$$C_6H_6 + Hal-\overset{-}{C}u-\overset{+}{C}H_2 \rightarrow \ldots \rightarrow \text{(XVII)} + CuHal$$

(XVII)

Yields of up to 85% result[130] with the catalytic species CuBr, CuCl, or $CuCl_2$, the last-named apparently being reduced to CuCl; and yields of 10—20% result with CuI, Cu, or $CuSO_4$. This copper-catalysed reaction has advantages over an earlier method of converting benzene into cycloheptatriene, in which photochemically initiated decomposition of diazomethane was used. It enables pure 7,7-dideuterocycloheptatriene to be prepared.[132] When applied to alkyl-, halogeno-, or methoxy-substituted benzene, it affords the corresponding cycloheptatriene derivatives in yields of 35—75%.[133]

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[133] E. Muller, H. Fricke, and H. Kessler, *Tetrahedron Letters*, 1963, 1501.