Metal-catalysed halogen exchange reactions of aryl halides

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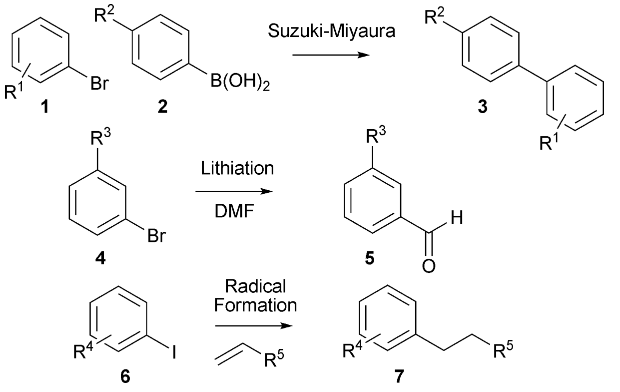
Aryl halides are common synthetic targets themselves, and also highly versatile synthetic intermediates. Aryl chlorides are much more widely available and easier to synthesise than the other halide derivatives, so the development of effective methods for interconverting aryl halide derivatives would therefore be extremely useful. This article outlines which transformations are particularly desirable, and describes the progress that has been made on developing methods for carrying out those transformations using copper, nickel or palladium catalysts. The possible mechanisms of these reactions are discussed, with a view to identifying areas for future investigation.

Introduction

Aryl halides are highly useful synthetic intermediates which have many applications in organic chemistry. The aryl halide functional group can readily be exploited in a wide range of cross-coupling reactions, be used for the formation of organometallic reagents or act as a precursor for the generation of free-radical intermediates (Scheme 1).

Aryl halides are often important synthetic targets in their own right, as illustrated by the pharmaceuticals and agrochemicals shown in Fig. 1. The regioselective synthesis of aryl halide derivatives containing radioactive halogen isotopes is also of great importance for medical applications (e.g. introduction of ^{18}F labels for PET).[1,2]

The properties of aryl halides are highly dependent on the nature of the halogen atom. The bond strength of the C–X bond decreases significantly as the size of the halogen atom increases from F to I (Table 1).



Scheme 1 Useful reactions of aromatic halides.

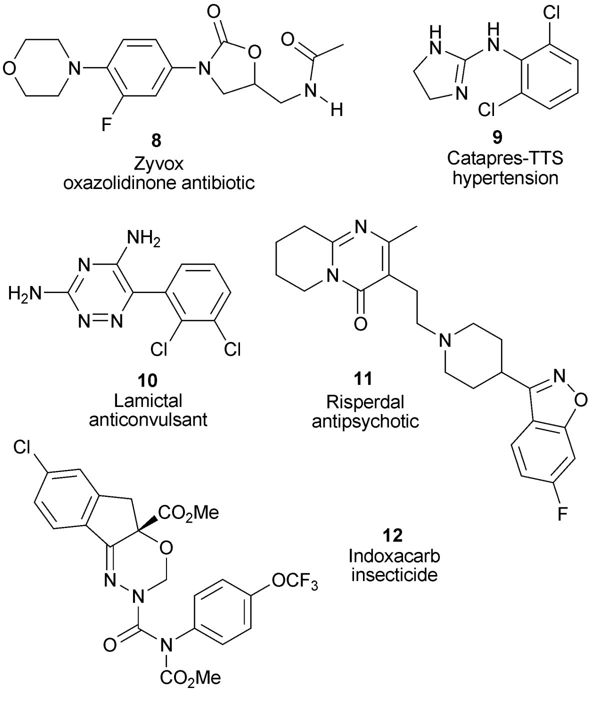


Fig. 1 Aryl halide pharmaceuticals and agrochemicals.

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Tom Sheppard was born in Preston, Lancashire, in 1977. He obtained his MSci degree from the University of Cambridge in 1999. After a year working at GlaxoWellcome, he went on to obtain his PhD from the University of Cambridge under the supervision of Professor Steven Ley. He then carried out postdoctoral research with Professor William Motherwell at University College London. In 2007, he was awarded an EPSRC Advanced Research Fellowship and appointed to a lectureship at University College London where his research interests include the development of novel organocatalytic and metal-catalysed reactions.

Table 1 Bond dissociation energies of aryl halides

Bond	Dissociation energy (kJ mol^{-1})
Ph–F	533
Ph–Cl	407
Ph–Br	346
Ph–I	280

Potentially useful transformations

Aryl iodides and bromides are generally much more reactive than chlorides and fluorides, and can readily be employed in all of the chemical reactions described above (Scheme 1), with iodides being more reactive due to the weaker C–I bond. Chlorides and fluorides, however, are generally relatively inert and, as a consequence, they are much more commonly found in pharmaceuticals and agrochemicals, where they are introduced to modify the physical and biological properties of aromatic rings. Fluorides are often particularly important, but there are very few industrially viable methods for the introduction of fluorine atoms into an aromatic ring. Typically, aryl fluorides are either bought in as starting materials, or the fluoride must be introduced *via* an S_NAr reaction or diazotisation chemistry. Sulfonate esters derived from phenols can be employed as alternatives to aryl halides in many cross-coupling reactions, and these are often referred to as 'pseudo-halides'. Typically, an aryl triflate shows similar reactivity to an aryl bromide in these reactions. Such pseudo-halides, however, cannot be employed for the generation of organometallic reagents or free-radicals.

The most readily accessible compounds are aryl chlorides and a vast range of these are available commercially. Similarly, many pseudo-halides can also be readily accessed from the wide range of commercially available phenols. Fewer fluorides, bromides and iodides are available, and it would therefore be extremely useful to have a general method for *interconverting* between the different halogen derivatives – an alternative to the Finkelstein reaction, which is widely used to interconvert alkyl halides through an S_N2 mechanism.[3] The most potentially useful transformations are:

I Conversion of readily available aryl chlorides into the more reactive bromides and iodides.

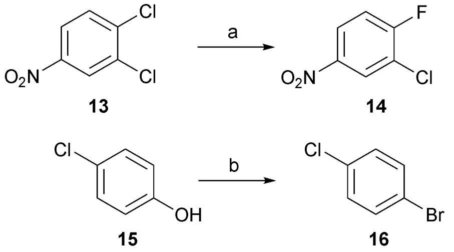
II Conversion of readily accessible sulfonate esters into bromides or iodides for use in the generation of organometallic reagents or free-radicals.

III Conversion of more easily accessible halides and sulfonates into aryl fluorides, which are difficult to synthesise by other methods.

IV Direct halogenation of an aromatic ring, *via* a transition-metal-mediated C–H activation process.

Possible mechanisms

Direct nucleophilic substitution of a halogen atom at an sp^2 centre is not readily achievable due to the inaccessibility of the C–X antibonding orbital. Substitution *via* an S_NAr mechanism is possible on electron-deficient compounds, and this is an important method for the preparation of aryl fluorides[4–7] (Scheme 2, **13**).[8] On more electron-rich systems however, substitution processes have a very high activation energy. For example, 4-chlorophenol **15** can be brominated using PPh_3Br_2 but a reaction temperature of 200 °C is required,[9] presumably because the required transition state involves significant disruption of the aromatic system.



Scheme 2 a. KF, Me_4NCl, DMSO, 120 °C, 99%; b. PPh_3Br_2, 200 °C, 90%.

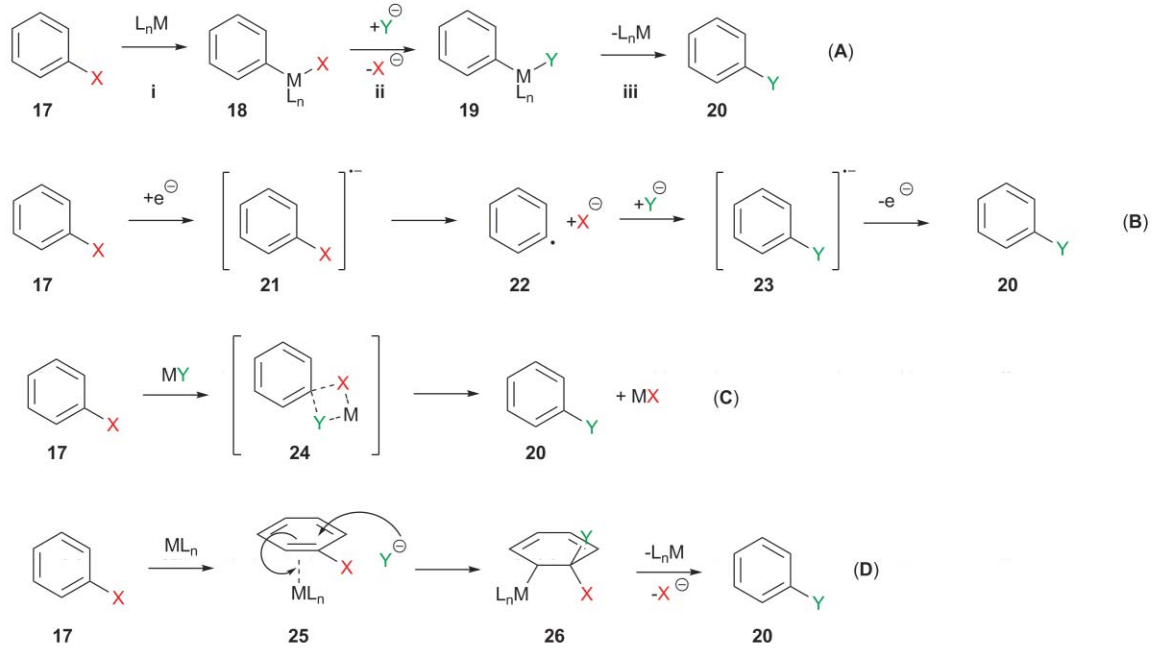
A viable process for aromatic halogen exchange must therefore proceed *via* an alternative mechanism. An obvious solution is a transition-metal-catalysed process which could operate *via* a variety of mechanisms including both one- and two-electron pathways (Scheme 3, Paths A–D).

Perhaps the most logical approach is a typical cross-coupling pathway (Path A, Scheme 3). Thus, oxidative addition of an aryl halide **17** to a transition-metal catalyst (**i**), can be followed by ligand exchange (**ii**) to give the complex **19**. Finally, reductive elimination (**iii**) of the product **20** will regenerate the active catalyst. This overall transformation is similar to that of the nickel-catalysed displacement of halides by cyanide, a variant of the Rosemund–von Braun reaction.[10] However, a general transformation has yet to be developed for aromatic halogen exchange. It is therefore of great importance to obtain an understanding of the many factors which affect the steps **i**–**iii**. The oxidative addition of all types of aryl halides and pseudo-halides to transition-metal complexes (**i**) has been reported, and this process is generally well understood for metals such as palladium. Similarly, exchange of halide ligands at the metal centre has been used to synthesise a variety of complexes, and this process is generally considered to be rapid. In contrast, relatively little is known about the reductive elimination of an arylmetal halide complex to give an aryl halide (**iii**).[11] The very recently reported mechanistic studies by Buchwald and Roy constitute the first direct observation of this process at Pd(II) (Scheme 4).[12–14] Counter-intuitively, the reductive elimination is promoted by addition of a very electron-rich phosphine ligand to the dimeric complex **27**, such ligands normally being used to promote the reverse oxidative-addition process. The authors attribute the promotion of the reductive elimination reaction to the large steric bulk of the ligand, rather than its electronic properties. The equilibrium constants for the reductive elimination of Ar–Cl, Ar–Br, and Ar–I from the complex **30** were measured and are shown in Table 2.

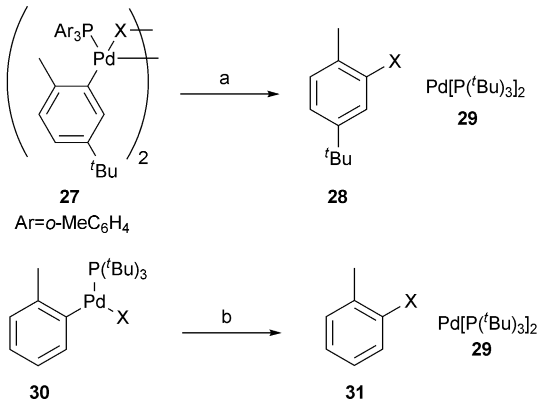
Table 2 Equilibrium constants for the reductive elimination of aryl halides from palladium complex **30**

Aryl halide	K_{eq}[a]
Ar–Cl	1090
Ar–Br	3.27
Ar–I	0.179

[a] Values are referenced to a 1 M standard state.



Scheme 3 Possible mechanistic pathways for a transition-metal-catalysed halogen exchange reaction.



Scheme 4 a. $P(^tBu)_3$ (15 eq), C_6D_6, 70 °C, 70% (X = Cl, Br), 39% (X = I); b. $P(^tBu)_3$ (20 eq), C_6D_6, 70 °C, 76% (X = Cl), 98% (X = Br), 79% (X = I).

Interestingly, although the reductive elimination of the aryl chloride is the most favourable process thermodynamically, presumably due to the higher bond strength of the C–Cl bond, this process is kinetically much slower than the reductive elimination of Ar–Br or Ar–I.[12–14] These results suggest that a general palladium-catalysed halogen exchange reaction should be feasible, as the necessary reductive elimination step can take place. However, the reverse process of oxidative addition is normally overwhelmingly favoured under typical reaction conditions for palladium catalysis. A lot of work still needs to be done in order to establish practical conditions under which both steps occur readily, enabling an efficient halogen exchange process to take place.

Constrastingly, a considerable amount of effort has been directed towards the study of reductive elimination of aryl fluorides from palladium, with little success. Although a variety of arylpalladium fluorides have been prepared and studied, the reductive elimination of Ar–F appears to be a very unfavourable process.[15,16] When heated under forcing conditions, the formation of P–F or C–P bonds *via* reductive elimination is usually observed, rather than the desired C–F bond formation. There is a single example of the formation of a small quantity of aryl fluoride on heating an arylpalladium fluoride complex,[17] but this involves the formation of 4-nitrofluorobenzene, and the involvement of an S_NAr-like process cannot be wholly discounted.[15]

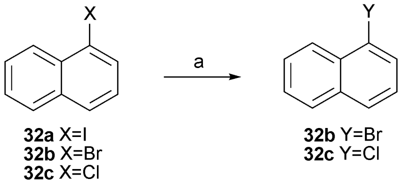
Substitution of aryl halides can also occur *via* a variety of single-electron transfer processes such as the $S_{RN}1$ reaction[18] (Scheme 3, Path B). In this process, an electron is transferred to the aryl halide to generate a radical anion **21**. This can dissociate into an aryl free-radical **22** and a halide ion, before reaction with the nucleophile to generate the radical anion **23** of the product. This in turn can then undergo single-electron oxidation to give the final product **20**. $S_{RN}1$ reactions are generally initiated either by UV irradiation of the reaction mixture in ammonia solution, or by a transition-metal catalyst such as $FeCl_2$. Path C (Scheme 3) illustrates a 4-centre transition state **24** which has been proposed for certain metal-catalysed reactions of aryl halides. Finally, an S_NAr-like pathway can be envisaged in which the metal catalyst forms a complex **25** with the aromatic ring system, facilitating the attack of the nucleophile Y (Scheme 3, Path D). The complexation of the aromatic ring to the cationic metal centre might be expected to reduce the electron density on an electron-rich aromatic ring, thus rendering it susceptible to nucleophilic attack. In theory, any of these mechanisms could be harnessed to provide a successful halogen exchange process by adding an excess of halide Y to drive the reaction towards the formation of the product **20**.

Methods for aromatic halogen exchange

Copper

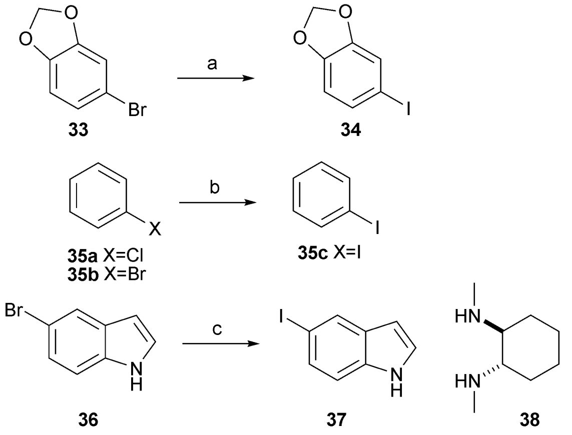
Copper-catalysed substitution of aromatic halides with a variety of nucleophiles has been known for a very long time. The earliest examples of halogen exchange reactions were reported in the 1960s, by heating aryl halides in the presence of copper(I) halide salts in a range of polar solvents.[19]

In terms of the reactivity of aryl halides, it was found that Ar–I > Ar–Br > Ar–Cl. Similarly, CuCl was found to be more reactive than CuBr or CuI. Under these conditions, the reaction is only preparatively useful for the preparation of chlorides (**32c**) from bromides (**32b**) or iodides (**32a**), and the preparation of bromides from iodides, neither of which are usually synthetically useful (Scheme 5). An alternative procedure using copper(I) oxide as a catalyst in the presence of lithium, sodium or quaternary ammonium halides was slightly more general, although only low conversions were obtained for reactions in the 'reverse' direction (e.g. a 7% yield of **32a** was obtained from reaction of **32b** with NaI).[20] The formation of vinyl chlorides from vinyl bromides, using copper(I) halide–phosphine/phosphite complexes, has also been reported.[21]



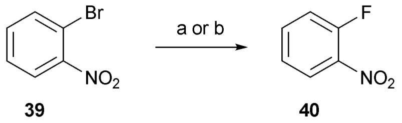
Scheme 5 a. CuY, pyridine, 115 °C, 84% (X = Br, Y = Cl), 100% (X = I, Y = Br), 5% (X = Cl, Y = Br).

In later work, examples of preparatively useful 'reverse' halogen-exchange reactions were reported in which more reactive aryl iodides were prepared from aryl bromides or chlorides. Iodides can be obtained from bromides by heating a mixture of aryl bromide, CuI and KI in HMPA (Scheme 6, **34**).[22,23] More usefully, aryl iodides can be obtained from either bromides or chlorides by treatment with an alumina or charcoal-supported CuI reagent at 130–150 °C (Scheme 6, **35c**), although extended reaction times were required in the latter case.[24,25] Recently, Buchwald and Klapars reported that diamino ligands such as **38** were able to promote copper-mediated halogen-exchange processes, and a practical procedure for converting aryl bromides to aryl iodides with only 5 mol% CuI was developed (Scheme 6, **37**).[26] Unfortunately, the conditions led only to very slow reaction of aryl chlorides (35% conversion of chlorobenzene after 24 hours). However, the conditions were applicable to a range of functionalised aromatic and heteroaromatic bromides. A copper-mediated halogen-exchange of this type was recently employed in a three-component reaction sequence for the synthesis of 1,4-diamidobenzenes.[27]



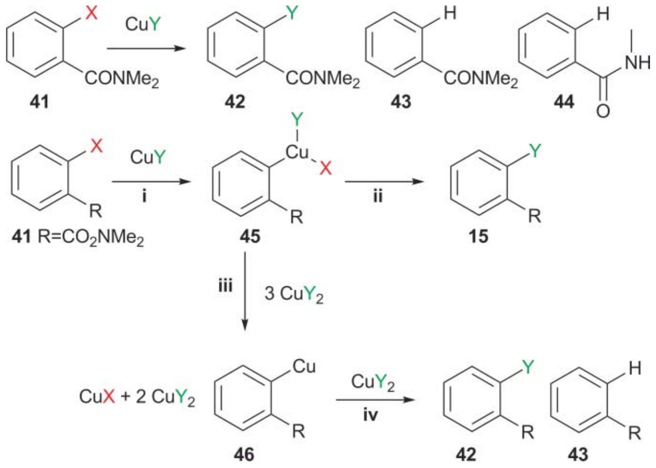
Scheme 6 a. KI (15 eq), CuI (5 eq), HMPA 150–160 °C, 71%; b. alumina–CuI, neat, 150 °C or 130 °C, 94% (X = Br), 58% (X = Cl); c. CuI (5 mol%), **38** (10 mol%), NaI (2 eq), dioxane, 110 °C, 98%.

There is also a single report of copper-mediated fluorination by reaction of 2-bromonitrobenzene with potassium fluoride and the copper(I) complex $(Ph_3P)_3CuF$ (Scheme 7).[28] The reaction is apparently not just a simple S_NAr process, as reaction with KF under the same conditions led to very low yields of the fluorobenzene. However, the reaction has yet to be reported for other aromatic substrates so is currently of limited utility.



Scheme 7 a. KF, $(Ph_3P)_3CuF$, DMF, reflux, quant. b. KF, DMF, reflux, 5%.

A number of different mechanisms for the copper-mediated activation of an aryl halide have been proposed, including a 4-centred transition state (Scheme 3, Path C), an oxidative addition reaction to form a copper(III) intermediate (Scheme 3, Path A), copper mediated S_NAr *via* formation of a π-complex (Scheme 3, Path D), and single-electron transfer processes such as $S_{RN}1$ (Scheme 3, Path B). Common by-products from the reaction include reduced products and dimers, which led initially to the suggestion that aryl radicals were intermediates. However, on the basis of a number of radical trapping experiments, the intermediacy of aryl free-radical species or radical anions of the aryl halides seems very unlikely.[29] The amide **44** (Scheme 8) is obtained as a major product when an adjacent radical is generated on the aromatic ring (e.g. from Cu-catalysed decomposition of a diazo compound), being formed *via* intramolecular hydrogen abstraction and subsequent hydrolysis. This product was not observed in the Cu(I)-mediated halogen exchange reaction of **41**.



Scheme 8 Possible mechanistic pathways for Cu(I)-mediated halogen exchange reactions.

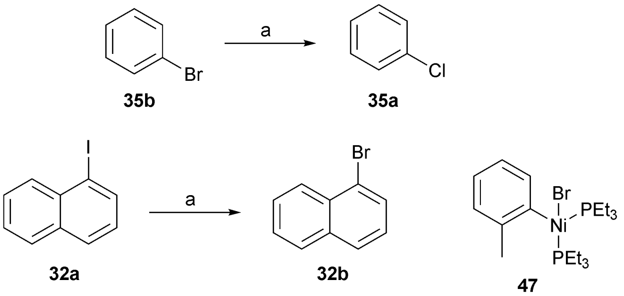
Similarly, the order of reactivity of aryl halides (I > Br > Cl) is inconsistent with an S_NAr-like process proceeding *via* a π-complex.

As a consequence, the formation of a copper(III) intermediate by oxidative addition of the aryl halide to copper(I) seems most likely (Scheme 8, **i**). The halogen exchange process could then proceed by ligand exchange and reductive elimination (Scheme 8, **ii**) as for Path A in Scheme 1, although Cohen and co-workers suggested a more complex process in which the arylcopper(III) intermediate reacts with $CuCl_2$ present in the reaction mixture to generate ArCu (Scheme 8, **ii**),[30] which then reacts further with $CuCl_2$ to give the exchanged product (**iv**). This proposal was based on the observation that the product ratio of aryl chloride to aryl (**42**:**43**) was found to increase in direct proportion to the concentration of $CuCl_2$. Similarly, this product ratio (**42**:**43**) decreased in proportion to the concentration of benzoic acid present as an additive. They proposed that an aryl copper species **46** is formed, which reacts with $CuCl_2$ to give the product **42**, and is protonated by benzoic acid to give compound **43**. However, van Koten and co-workers subsequently disputed this mechanism on the grounds that it is inconsistent with the known chemistry of ArCu species.[31] In addition, they also reported that reaction of ArCu with $CuCl_2$ led to the formation of large quantities of homo-coupled product (Ar–Ar), together with small quantities of chloride and arene.

As can be seen from these studies, the mechanism of these copper-mediated halogen exchange reactions is far from clear, but a pathway proceding *via* oxidative addition of the aryl halide to generate an ArCu(III)XY species, followed by reductive elimination of the ArY product, seems the most likely possibility. This pathway is similar to the mechanisms proposed for a range of other copper-mediated aromatic substitution reactions.[32] However, the oxidative addition seems to be dependent on the high affinity of copper for halogen atoms, as no copper-mediated exchange reactions of aryl sulfonates have yet been reported.

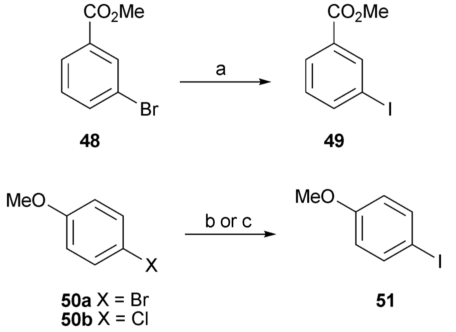
Nickel

Nickel-mediated halogen exchange reactions were first reported by Cramer and Coulson.[33] They observed that $NiCl_2$ catalysed the formation of chlorobenzene from bromobenzene and lithium chloride in EtOH at 210 °C, even at very low catalyst loadings (Scheme 9). The reaction was also successful in DMF. Kochi and Tsou subsequently carried out a more detailed study of the reaction.[34] In their mechanistic investigation, they observed that the halogen exchange reaction between aryl halides and quaternary ammonium halides could be catalysed by a variety of nickel complexes. Phosphine ligands were found to be important for efficient exchange reactions to take place, and they employed complexes of the general structure $ArNiX(PEt_3)_2$ as catalysts in their reactions. Efficient exchange took place between the two halide sources, and the reaction of iodobenzene/Bu_4NBr or bromobenzene/Bu_4NI was found to reach equilibrium in the presence of small quantities of nickel catalyst **47** (Scheme 9). The formation of aryl bromides from iodides could be observed with a wide range of *ortho*-, *meta*- and *para*-substituted systems, in the presence of 3 mol% catalyst in benzene solution at 80 °C. The reaction could also be carried out in THF and to some extent DMF, although ethanol, DMSO and acetone were less effective.



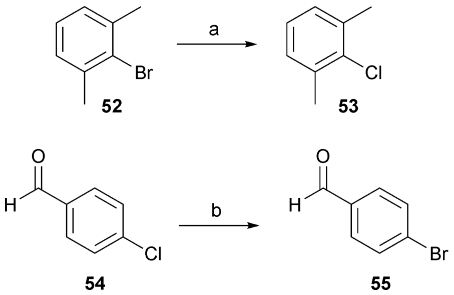
Scheme 9 a. LiCl, $NiCl_2$ (0.001 mol%), 68% (EtOH, 210 °C), 77% (DMF, 157 °C); b. **47** (3 mol%), Bu_4NBr (1 eq), PhH, 80 °C, 74%.

Simultaneously, preparatively useful reactions for preparing aryl iodides from bromides were reported by Takagi and co-workers (Scheme 10, **49**).[35,36] They employed a mixture of Ni(II) salt, potassium iodide and zinc powder in polar solvents such as HMPA at 50 °C. The reaction was proposed to proceed *via* in situ generation of a Ni(0) species which can insert into the aryl bromide, and undergo halogen exchange *via* Path A. Due to the requirement for a large excess of Zn powder for effective initiation to take place, homo-coupled Ar–Ar by-products were always obtained, and the best yields of aryl iodides were obtained by stopping the reaction before completion in order to minimise the quantity of aryl iodide product lost *via* the homo-coupling reaction. A subsequent report by Cheng and co-workers used commercially available nickel powder directly in halogen exchange reactions with KI (Scheme 10, **51**).[37] The Ni(0) powder was considerably less active than *in situ*-generated Ni(0) (reactions were carried out in DMF at 150 °C), but Ar–Ar homo-coupled products were not observed under these conditions. Aryl iodides could be readily prepared from aryl bromides, and to a lesser extent, from aryl chlorides.



Scheme 10 a. KI (2.5 eq), cat. $NiBr_2$, Zn, HMPA, 50 °C, 81%. b. Ni(s), KI (2 eq), DMF, 150 °C, 76% (X = Br). c. Ni(s), NaI (5 eq), DMF, 150 °C, 55% (X = Cl).

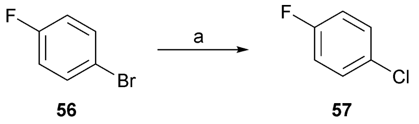
More recently, a more general nickel-mediated halogen exchange procedure was reported in which an aryl halide is heated at 170 °C in DMF in the presence of a stoichiometric quantity of a Ni(II) salt (Scheme 11).[38] The reaction works reasonably well for both the formation of aryl chlorides (**53**) from bromides or iodides, and the formation of aryl bromides (**55**) from aryl chlorides. It was also reported that the reaction can be carried out conveniently under microwave irradiation. Catalytic quantities of $NiBr_2$, in the presence of an equivalent of NaI, have also been successfully used to activate aryl chlorides for Heck reactions, despite the fact that



Scheme 11 a. $NiCl_2$ (2 eq), DMF, 170 °C, μw, 99%. b. $NiBr_2$ (2 eq), DMF, 170 °C, μw, 41%.

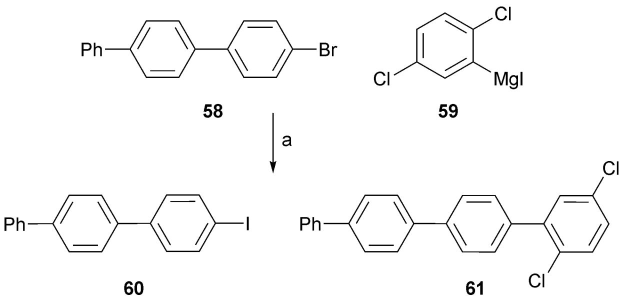
only around 5% of the aryl chloride was converted to the iodide under the reaction conditions.[39]

An unusual Ni(II)-catalysed halogen exchange reaction was reported by O'Connor and Burrows in which a nickel catalyst was used to mediate the conversion of aryl bromides into aryl chlorides in the presence of NaOCl (Scheme 12).[40] The reaction was carried out in an aqueous–organic solvent mixture at ambient temperature, in the presence of a phase-transfer catalyst. The reaction was proposed to proceed *via* the generation of chlorine free-radicals, which react with the bromoarenes *via* a free-radical *ipso* substitution reaction. Evidence for the presence of Cl radicals included the competing halogenation of benzylic positions on alkyl-substituted benzenes. Unfortunately, the reaction conditions could only be used to prepare chlorides from bromides. Attempts to carry out either the reverse reaction, or even the preparation of chlorides from iodides, were unsuccessful.



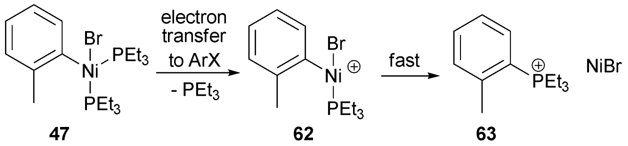
Scheme 12 a. cat. Ni(TPP), $BnNBu_3Br$, NaOCl, pH 9, H_2O, $CHCl_3$, 100%.

Finally, nickel-mediated halogen exchange between an arylmagnesium iodide and an aryl bromide has been reported as a significant side-reaction during an attempted cross-coupling reaction (Scheme 13).[41] The mechanism appears to be complex, however, and the process was not reported to be generally applicable. Nevertheless, it suggests that treatment of a Ni(II) salt with an aryl Grignard reagent produces a catalytic species which is capable of mediating halogen exchange between essentially inorganic iodide and an aryl bromide. Notably, the iodide **60** is more reactive than the starting bromide in the cross-coupling reaction with **59** to produce **61**, and hence large quantities of the iodide must be produced after complete consumption of the Grignard reagent.



Scheme 13 a. cat. $NiCl_2$, THF, 50–65 °C, 38% (**60**), 26% (**61**).

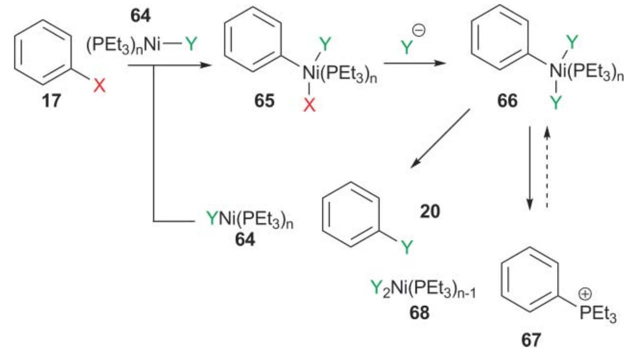
The mechanism of Ni(II)-catalysed halogen exchange processes was studied in considerable detail by Kochi and Tsou, by carrying out the reaction of an aryl halide (ArY) with a stoichiometric quantity of the complex $ArNiX(PEt_3)_2$.[34] In all cases, the reaction exhibited an induction period of between 2 and 80 minutes, after which rapid halogen exchange took place (complete in <2 min). This induction period could be extended by adding additional phosphine ligand (PEt_3), or reduced by adding $NiBr_2$. The induction period was therefore interpreted as the reaction time necessary for the formation of the catalytically active species, which was proposed to be a Ni(I) complex. This can be formed by electron transfer to the aryl halide from the Ni(II) complex, and subsequent reductive elimination of an arylphosphonium salt. (Scheme 14).



Scheme 14 Proposed formation of the Ni(I) catalytic species.

This is consistent with the effects of additional ligand or nickel salt on the induction period, as the formation of a nickel(I) complex is dependent on the dissociation of one of the phosphine ligands from the $ArNiX(PEt_3)_2$ complex **47**. This process is therefore accelerated by adding a small quantity of phosphine scavenger such as $NiBr_2$. Methyl triflate was also shown to reduce the induction period, presumably by alkylation of some of the excess phosphine present in the reaction mixture. Similarly, addition of excess phosphine would be expected to slow down the formation of the nickel(I) species. Further evidence was obtained by demonstrating that the preformed Ni(I) complex $NiBr(PEt_3)_3$ catalysed the reaction between PhI and Bu_4NBr extremely effectively and without a lengthy induction period. Most of the other reported nickel-catalysed halogen exchange reactions (Schemes 10, 11 and 13) could also involve Ni(I) catalysis, as both reduction of an aryl halide with Ni(0) and reduction of Ni(II) with zinc or a Grignard reagent could plausibly lead to the generation of Ni(I) intermediates.

However, the exact mechanism by which a Ni(I) complex can catalyse the reaction is uncertain. Both a four-centre transition state (Scheme 3, Path C) and a standard oxidative addition–reductive elimination cycle involving Ni(III) intermediates (Scheme 3, Path A) were proposed. The authors suggested that the latter option may be less likely, as such Ni(III) intermediates are known to produce arylphosphonium salts *via* reductive elimination. However, it may simply be that a nickel(I) species is able to mediate many cycles of halogen exchange before phosphonium salt reductive elimination takes place. The oxidative addition of an aryl halide to the Ni(I) complex **64** will give a Ni(III) complex **65**, which in the presence of excess halide Y is expected to form **66** (Scheme 15). This complex can then undergo either reductive elimination of the product ArY **20** to regenerate the catalytic Ni(I) species **64**, or reductive elimination of phosphonium salt **67**, which leads to the formation of a Ni(II) species **68** similar to the pre-catalyst. The latter reductive elimination could also be a reversible process, as scrambling of the aryl groups present on phosphorous ligands has been observed in a variety of transition-metal-catalysed reactions. This is thought to take place *via* a cycle of reversible reductive eliminations of phosphonium salt.[42,43] A four-centre direct displacement (Scheme 3, Path C) seems less likely from our current knowledge of transition-metal chemistry.

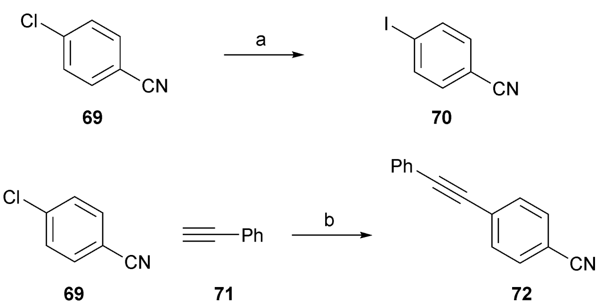


Scheme 15 Plausible mechanism for Ni(I)-catalysed halogen exchange.

Palladium

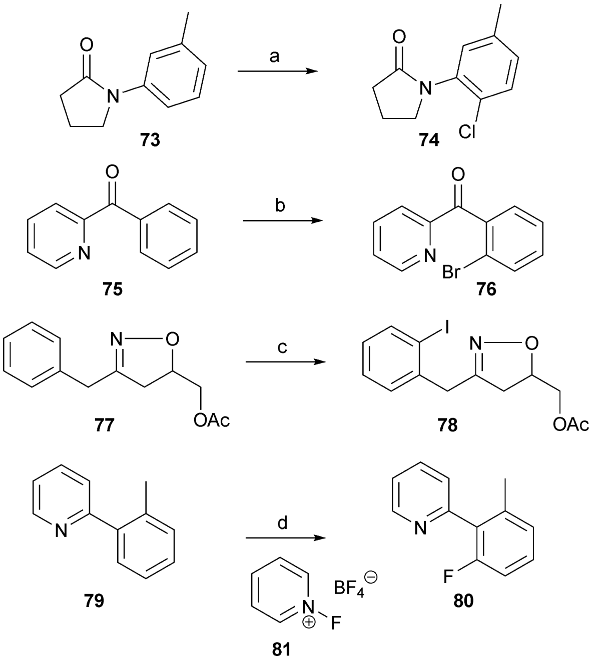
Although there has been a vast amount of research directed towards understanding and improving the many palladium-catalysed cross-coupling reactions, there are virtually no reports of palladium-catalysed halogen exchange. Most research effort is currently directed towards developing ligands and reaction conditions which enable less reactive aryl chlorides to be employed in cross-coupling reactions.[44] However, whilst there has been considerable success in this area, there are still no mild methods for the generation of free-radicals from aryl chlorides, or their conversion into organometallic reagents. A method to convert aryl chlorides into the more reactive bromides or iodides is therefore still desirable. In principle, a palladium-catalysed halogen exchange process could be envisaged which proceeds *via* a standard catalytic cycle (Scheme 3, Path A), but this has not been reported. As we have already seen, until recently there were no published studies of the reductive elimination of an aryl halide from palladium, and this step is certainly the least well understood part of the proposed catalytic cycle.[11]

In a recent report, Pd/C was used to catalyse the formation of aryl iodides from a limited range of aryl chlorides and sodium iodide in DMF at 130 °C (Scheme 16).[45] This procedure was then applied to a direct one-pot Sonogashira coupling reaction of aryl chlorides, which was demonstrated to proceed *via* the intermediate aryl iodide. Unfortunately, this convenient procedure for halogen exchange was only applicable to electron-deficient aryl chlorides. Chlorobenzene did not react under the conditions, but more electron-rich *bromides* did undergo the tandem halogen-exchange Sonogashira reaction to some extent. Given the fact that electron-deficient arenes are more reactive under these conditions, it seems reasonable to assume that this exchange process may have an S_NAr-like mechanism in which the palladium activates the aromatic ring in some way. The possible catalytic effect of the charcoal support cannot be excluded, as this has been shown to be beneficial in other halogen substitution reactions.[25,46]



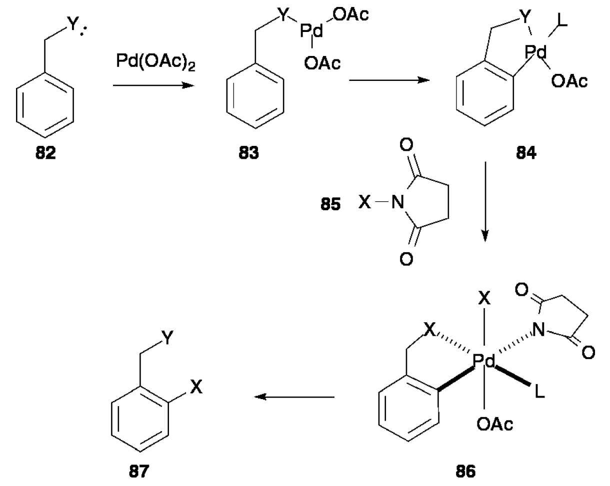
Scheme 16 a. KI (3 eq), Pd/C (3 mol%), DMF, 130 °C, 64% conversion; b. KI (3 eq), **71** (1.5 eq), KF (2.5 eq), DMF, H_2O, 130 °C, 58%.

Although no generally successful palladium-catalysed halogen exchange reactions have yet been reported, there has been considerable success in the development of palladium-mediated direct halogenation of aromatic rings.[47–55] On systems which contain a suitable directing group to facilitate reaction of the metal centre with an aryl C–H bond, any halogen atom (I, Br, Cl or F) can be introduced regioselectively by choice of a suitable halogenating agent (Scheme 17). Treatment of a suitable aromatic substrate with *N*-halosuccinimides (Cl, Br, I)[51,53] or the *N*-fluoropyridinium salt **81** (F),[52] in the presence of 5 mol% $Pd(OAc)_2$ in refluxing AcOH or MeCN, leads to good yields of the halogenated products, for example. These direct halogenation reactions provide an extremely useful method for direct halogenation of arene rings that is complimentary to existing methods. For example, the regioselectivity of the reaction is often different to traditional electrophilic halogenation reactions, and aryl halides can therefore be accessed that would otherwise be difficult to prepare.



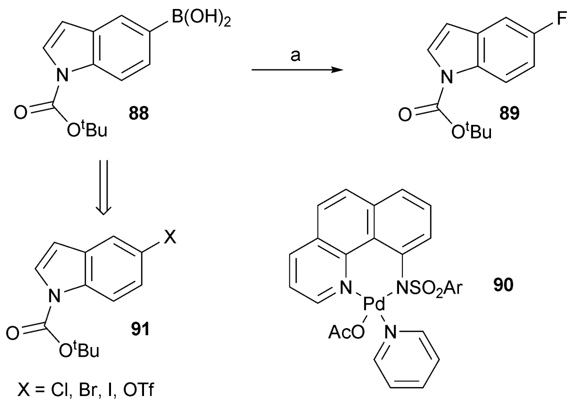
Scheme 17 a. $Pd(OAc)_2$ (5 mol%), NCS (1–1.5 eq), AcOH, 100 °C, 81%; b. $Pd(OAc)_2$ (5 mol%), NBS (1–1.5 eq), AcOH, 120 °C, 56%; c. $Pd(OAc)_2$ (5 mol%), NIS (1–1.5 eq), AcOH, 100 °C, 54%; d. $Pd(OAc)_2$ (10 mol%), **81** (2.5–4.5 eq), MeCN, CF_3Ph, 150 °C, μw, 81%.

It has been known for a long time that treatment of organopalladium(II) complexes with oxidising agents induces reductive elimination of functionalised organic molecules from the metal centre, and this has been used for the stoichiometric palladium-mediated functionalisation of unactivated C–H bonds in many cases.[56–59] There is very good evidence that the reactions in Scheme 17 proceed *via* a palladium(II)/palladium(IV) catalytic cycle. Thus, co-ordination of the directing group to the Pd(II) species facilitates C–H activation on the aromatic ring to give an arylpalladium species (Scheme 18, **84**). This is oxidised to a Pd(IV) complex **86** by the electrophilic halogenating agent **85**, and then undergoes reductive elimination to give the aryl halide product **87** and regenerate a catalytically active Pd(II) species. Whilst reductive elimination of an aryl halide from Pd(II) is a difficult process that requires forcing conditions, it is a considerably easier process from a more electron-deficient Pd(IV) species. Arylpalladium(IV) chlorides similar to the proposed intermediates have been prepared, and shown to undergo facile reductive elimination of aryl chloride on heating in acetic acid.[50]



Scheme 18 Proposed mechanism for Pd(II)-catalysed direct halogenation.

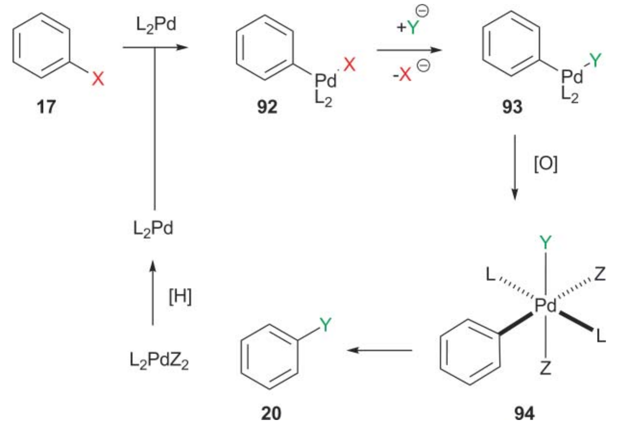
A similar approach has also been exploited as a method for direct fluorination of boronic acids (Scheme 19, **88**) by transmetallation to palladium complex **90** and then treatment with an electrophilic fluorine source. This potentially provides a 3-step method for converting any other aryl halide/pseudo-halide (e.g. **91**) into an aryl fluoride, as boronic acids can be readily accessed from a wide variety of aryl halides *via* metallation processes.[60]



Scheme 19 a. i) **90**, K_2CO_3, MeOH/PhH, 76%; ii) Selectfluor®, MeCN, 50 °C, 60%.

Currently, this method involves the use of stoichiometric palladium, but a catalytic reaction should be feasible *via* a similar cycle to that shown in Scheme 18, involving generation of the Pd(II) complex **84** by transmetallation from boron to palladium, rather than by C–H activation. This offers the advantage that the fluorine atom can be introduced into any position which has been functionalised with a boronic acid, rather than requiring the presence of an adjacent directing group.

This Pd(II)–Pd(IV) approach could potentially be adapted to a general halogen exchange protocol, if suitable conditions could be developed to initiate a catalytic cycle (Scheme 20), although this would be a somewhat ambitious undertaking.



Scheme 20 Possible mechanism for a Pd-catalysed halogen exchange.

Thus, oxidative addition of the starting halide ArX to Pd(0) would give complex **93** after halogen exchange. Oxidation of this complex to **94** would then induce the required reductive elimination, and regenerate a Pd(II) species that would have to be reduced to Pd(0) in order to begin another cycle. A catalytic oxidant (Z_2) would be required that can readily oxidise Pd(II) to Pd(IV), but can be regenerated on reduction of Pd(II) to Pd(0). Given that it is generally easier to oxidise Pd(0) to Pd(II) than it is to oxidise Pd(II) to Pd(IV), then this could be somewhat difficult to achieve. Alternatively, stoichiometric oxidising and reducing agents would be needed which were mutually compatible under the reaction conditions. A further possibility would be a sufficiently reactive Pd(II) species that can undergo direct oxidative addition of an aryl halide, and then halogen exchange could proceed *via* a Pd(II)–Pd(IV) cycle. This type of catalytic cycle has been proposed for a number of reactions,[61,62] but the intermediacy of arylpalladium(IV) intermediates remains to be proven.

Summary and outlook

Whilst a considerable number of methods for transition-metal-mediated halogen exchange have been reported, we are still far from developing methods for all the transformations **I**–**IV** identified above:

I The synthesis of aryl bromides/iodides from less reactive chlorides is possible using copper- or nickel-based methods, but harsh conditions are generally required. A search for better ligands that allow this reaction to take place at lower temperatures might enable this to become a more general process, which can be applied to more sensitive ring systems such as heterocycles. Certainly the conditions reported in Kochi and Tsou's mechanistic study are worthy of further investigation, as efficient reactions were observed at moderate temperature and with low catalyst loadings. If they can be adapted to use nickel catalysts which are more tolerant of air and moisture, then this could be a very effective approach.

II No methods have yet been developed for the conversion of aryl sulfonates into halides. As copper activation of aryl triflates is virtually unknown, a nickel- or palladium-mediated approach seems most plausible, as both of these metals can readily insert into aryl triflates. How this can be adapted into a halogen exchange reaction remains to be seen, however.

III The introduction of fluorine by replacement of another halogen atom is perhaps the most attractive transformation. However, only a single copper-based example has been reported, and this has not been extended to other substrates. In many of the published procedures for halogen exchange reactions, the authors note that no exchange was observed in the presence of fluoride ions. Clearly, the reductive elimination of aryl fluorides is not a straightforward process, as can be seen from the many studies of arylpalladium fluorides, and this step may well prevent any nickel- or palladium-mediated processes from being developed. The fact that a copper(I) fluoride complex has been successfully used in one case suggests that suitable conditions may be found for a more general copper-mediated fluorination of other aryl halides, and this area certainly merits further investigation.

IV Surprisingly, the development of transition-metal-catalysed direct halogenation of aryl C–H bonds has actually been very successful, despite the fact that at first glance this reaction seems the most challenging of the four transformations. Palladium-mediated methods for direct introduction of any of the four halogens have been reported, and these are successful on a wide range of substrates. There are obviously substrate limitations, due to the requirement for a suitable directing group to activate the C–H bond towards reaction, but the refinement of these methods and perhaps their extension to other metals will no doubt broaden the scope still further. A recent report on Cu-mediated C–H activation of aromatics is particularly interesting in this respect.[63]

It is clear that significant improvements could be made to many of the existing methods for halogen exchange in order to make them more generally applicable. There is considerable scope for the re-investigation and improvement of the older methods described above, and we can anticipate further breakthroughs to be made in the near future. In addition to copper, nickel and palladium, the investigation of other metals which can activate aryl halides, such as iron or platinum, might also be worthwhile.

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