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Key steps in the cross-coupling of organometallic compounds with organic halides, catalysed by nickel and palladium compounds

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ABSTRACT. The mechanism of cross-coupling of organometallic compounds with organic halides, catalysed by nickel and palladium complexes, has been examined. The key steps are discussed: oxidative addition, transmetallation, and reductive elimination. There is an analysis of the problems associated with the choice of the most effective ligands for the nickel and palladium complexes.

The bibliography contains 100 references.

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I. Introduction

A major problem in organic chemistry is the development of highly selective reactions in which carbon–carbon bond formation takes place. One such reaction is cross-coupling wherein organometallic compounds (notably of lithium and magnesium) interact with organic halides.

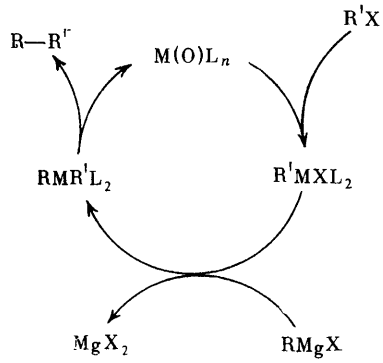
$$RM + R'X \rightarrow R{-}R' + MX. \quad (1)$$

However, cross-coupling has found a limited application in organic synthesis for two reasons: firstly, on account of concurrent elimination and exchange which leads to decrease in selectivity; and, secondly, on account of the inertness of organic halides possessing a halogen on an sp^2 atom. These limitations and associated practical difficulties can be overcome to a large extent by using organocopper compounds (in particular organocuprates) in place of organo-lithium or -magnesium reagents.[1,2] However, many problems remain unsolved. For example, cross-coupling with the formation of a carbon–carbon bond between sp^2 atoms proceeds with low selectivity; organic halides with reactive functional groups cannot always be used; and reactions with copper acetylides require fairly harsh conditions.

A new impulse to cross-coupling was given in the early 1970s when Kumada and Corrius et al.[3,4] demonstrated independently that cross-coupling of Grignard and organolithium compounds with alkenyl and aryl halides proceeds readily in the presence of nickel complexes. In 1975, it was shown[5] that the palladium complex, $Pd(PPh_3)_4$, is an effective catalyst for the reaction. Cross-coupling with more active organometallic compounds of (zinc,[6] aluminium,[7] zirconium,[8], boron,[9] tin [10] and mercury [11]) has significantly broadened the scope of the method, permitting the synthesis of various types of organic compound containing almost any functional group.

Since palladium- and nickel-catalysed cross-coupling proceeds under mild conditions in high yield and with high selectivity, the method has been widely applied in organic synthesis. Synthetic aspects of cross-coupling have been examined in earlier reviews.[12–17] This review is devoted to a detailed study of the mechanism of cross-coupling; a comparison is made of various organometallic compounds, RM in Eqn. (1), by considering the nature of the organic residues, R and R', and the metal, M; and the effect of the particular nickel of palladium catalyst has been studied.

For nickel- and palladium catalysed cross-coupling of Grignard reagents with organic halides, it is generally accepted that the mechanism of the reaction involves an initial oxidative addition of R'X to the zero-valent metal complex, M(0) followed by transmetallation with formation of a complex, $RMR'L_2$, having two σ-bonded organic residues; reductive elimination of R–R' completes the cycle with regeneration of M(0) [3,18] (scheme 2):



(2)

Nickel and palladium complexes are known to participate in the individual stages of this catalytic cycle. Thus, oxidative addition of aryl halides to PdL_4 leads to the formation of palladium σ-complexes, *trans*-$ArPdXL_2$.[19] By interaction of such complexes with RMgX, diorganopalladium complexes, *trans*-$ArPdRL_2$, are obtained. Some of these complexes have been isolated in pure form, e.g. where R = Me, Ph; Ar = *p*-FC_6H_4; L = PEt_3. In solution complexes $ArPdRL_2$ gradually cleave with the formation of cross-coupling product.[20] However, scheme (2) reflects only the most characteristic features of catalytic cross-coupling. There is no indication, for example, of the configuration of the mono- and di-organo-complexes, and no indication of the precise mechanism of the ligand exchange, etc. There is a detailed discussion below of

oxidative addition, reductive elimination, and transmetallation. Although cross-coupling is performed primarily in the presence of palladium and nickel catalysts, other transition metals will be considered with a view to elucidating general trends.

II. Oxidative addition

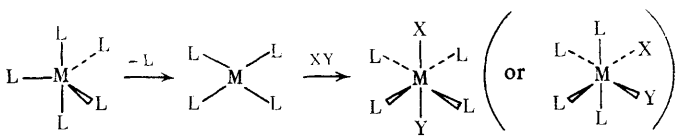
Oxidative addition is defined as the reaction of a transition metal complex with a substrate X–Y (H_2, O_2, RX, RH, etc.) wherein a covalent bond in the latter is cleaved with an associated one- or two-electron oxidation of the metal.[21]

$$X-Y+2M\rightarrow M-X+M-Y \text{ (or } X-M-M-Y) \quad (3)$$

$$X-Y+M\rightarrow X-M-Y \text{ (or } X-M^{+}Y^{-}) \quad (4)$$

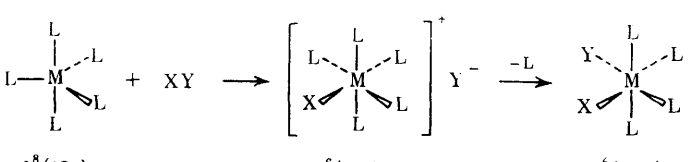
This reaction is characteristic of transition metal complexes in low oxidation states, especially complexes of Group VIII metals having a d^8- and d^{10}-electronic configuration. Oxidative addition is accompanied by a shift in the *d*-configuration from d^n to d^{n-1} or d^{n-2} with an increase in the coordination number. The reverse process, known as reductive elimination, is characterised by a decrease in the oxidation state of the transition metal. Clearly, it is because transition metals are able to exist in a number of oxidation states and are able to transfer easily from one oxidation state to another that they catalyse many reactions. On the contrary, oxidative addition and reductive elimination are quite uncharacteristic of non-transition metals. Thus, the latter do not catalyse cross-coupling. It should be pointed out that the term, oxidative addition, describes only the result of reacting X–Y with a transition metal complex, and is not a mechanistic definition.

In order to participate in oxidative addition, the transition metal complex may be either coordinatively saturated or unsaturated. The reactivity of coordinatively unsaturated complexes is, as a rule, significantly higher. There is an initial ligand dissociation on interaction of substrates, XY, with 5-coordinate 18-electron metal complexes with a d^8-configuration.



(5)

Coordinatively saturated d^8-complexes interact only with reagents having powerful oxidising properties. Reaction proceeds via intermediate formation of an octahedral cationic d^6-complex.

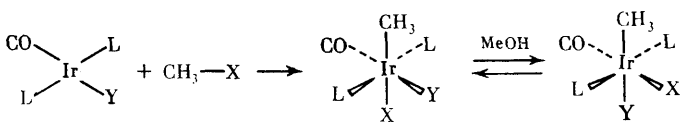


(6)

For substrates, XY, participating in oxidative addition one can designate three classes: class A are polar, electrophilic reagents; class B are reagents in which the bond between X and Y remains intact after oxidative addition; and class C are non-polar reagents.[21] Halogens (X_2), acids (HY), RSCl, RSO_2Cl, RX, RCOX, R_FI, RCN, $SnCl_4$, and HgX_2, for example, belong to class A; O_2, S_2, Se_2, *o*-quinones, RC≡CR, RN=NR, RCH=CHR, CS_2, CH_2O, cyclopropanes, $RCON_3$ and RN_3 are in class B; and H_2, R_3SiH, R_3GeH, R_3SnH, RSH, RCHO, ArH and RH are in class C. Of the multitude of oxidative oxidations,[21] we shall examine below only reactions involving organic halides (class A) in the presence of transition metal complexes.

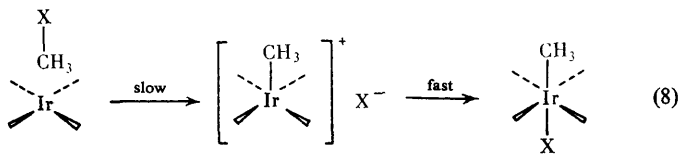
As low-valent transition metal complexes are basically nucleophilic, they readily react with alkylating agents. However, in contrast with familiar nucleophilic reagents, zero-valent metal complexes do interact with aryl and alkenyl halides. In mechanistic terms, reaction may involve an S_N2-process, a radical chain process, or a single-electron transfer (SET), depending on the formal charge on the metal complex, the nature of the metal, the ligand environment, the structure of the organic halide, and on the conditions under which oxidative addition is performed.

The oxidative addition of methyl halides to an iridium(I) complex is representative.



(7)

A kinetic study has shown that the reaction is of the second order (first order in each reactant).[22] The rate of the reaction increases with solvent polarity, being in the order: DMF > MeCN > THF > C_6H_5Cl > C_6H_6; and the large negative entropy of activation accords with an S_N2 mechanism for nucleophilic substitution of a carbon atom. It should be pointed out that it was not possible to intercept the 5-coordinate cationic iridium(III) intermediate (scheme 8) with an external nucleophile.[23]



(8)

A *trans*-methyliridium(III) complex is formed in non-polar solvents as a result of oxidative addition. In methanol the *trans*-complex isomerises to the thermodynamically more stable *cis*-complex.[24] A radical chain mechanism was excluded since the rate of oxidative addition is unaffected in the presence of radical traps.

The rate of reaction (7) increases with the basicity of the phosphine ligand L:

$$PEt_3 > PEt_2Ph > PEtPh_2 > P(p\text{-Tol})_3 > PPh_3.$$

However, in a number of cases, a steric effect can be the dominant factor.[25] For example, complexes where L = $PPhMe_2$ are more active than those where L = PEt_3. Evidently, this would also explain the higher rate of oxidative addition of CH_3X to the complex $FIrCOL_2$ than to $IIrCOL_2$.

Ethyl iodide is significantly less reactive than methyl iodide, and secondary alkyl halides in general do not participate in reaction (7) in the absence of a radical initiator. These results are also consistent with an S_N2 process.

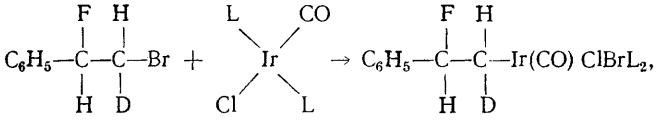
Secondary, and even primary, alkyl halides which are inactive in S_N2 reactions readily react with Ir(I) complexes by a radical chain

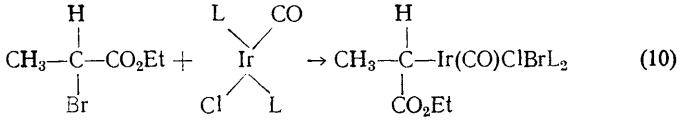
mechanism. This is confirmed by inhibition of the reaction with galvinoxyl and duroquinone, by the initiating effects of azodiisobutyronitrile and benzoyl peroxide, and by the fact that chiral substances are racemised.[26]

$$\left.\begin{array}{l} Q^{\cdot} + Ir(I) \rightarrow Ir(II)-Q \\ Ir(II)-Q + R-X \rightarrow X-Ir(III)-Q + R^{\cdot} \end{array}\right\} \text{initiation}$$

$$\left.\begin{array}{l} R^{\cdot} + Ir(I) \rightarrow R-Ir(II) \\ R-Ir(II) + R-X \rightarrow R-Ir(III)-X + R^{\cdot} \text{ etc.} \end{array}\right\} \text{chain extension} \qquad (9)$$

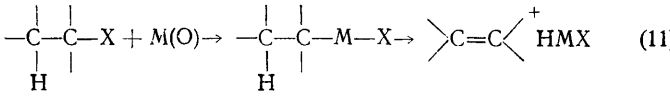
The stereochemistry of reaction (9) was studied using racemic diastereoisomers and pure enantiomers.[27]





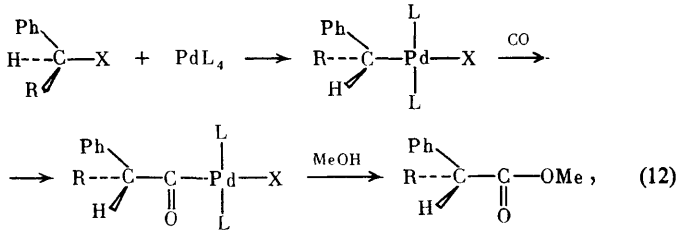
(10)

Oxidative addition involving d^{10} platinum and palladium complexes proceeds by an even more complicated pathway than reaction with Ir(I) complexes.[28] Alkyl halides which do not possess a β-hydrogen atom react with zero-valent palladium complexes to give stable alkylpalladium complexes.[29] However, with halides which do have a β-hydrogen atom, β-elimination of metal hydride takes place and the σ-alkyl complex is not isolated.



(11)

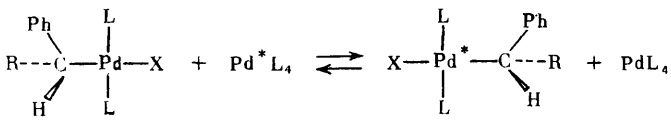
An S_N2-type mechanism prevails for reactions with palladium complexes since chiral benzyl halides react predominantly with inversion of configuration at the benzylic carbon atom.[30] Both primary and secondary benzyl halides react according to this mechanism.



(12)

R = D, CH_3; L = PPh_3.

It has been suggested that the observed partial racemisation is a consequence of a metal–metal exchange involving Pd(0) and Pd(II) complexes, rather than intervention of a radical process.[30]



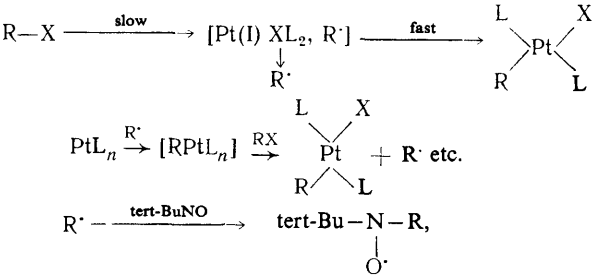
(13)

Alkylation of palladium complexes having the more basic phosphine ligand, L = PEt_3, also proceeds with inversion of configuration, but the optical yield is relatively low.[31]

With such halides as 9-bromofluorene, α-carbethoxybenzyl bromide, and trimethylsilylchloride, the corresponding dimers are obtained, rather than products derived via oxidative addition:[29]

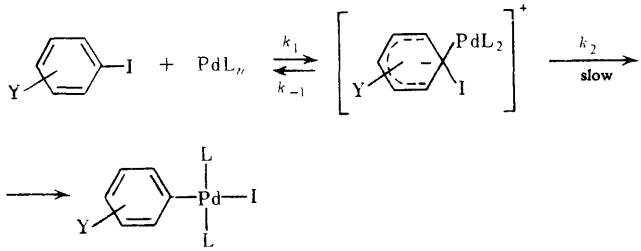
$$2RX + PdL_4 \xrightarrow[-2L]{} R-R + PdX_2L_2. \qquad (14)$$

In contrast to palladium(0) complexes, platinum(0) analogues react with organic halides essentially by a radical mechanism.[28,32,35] Thus, the reaction of n-butyl bromide with $Pt(PEt_3)_3$ is inhibited by galvinoxyl. It has been reported, in fact, that galvinoxyl interacts with a Pt(0) complex.[28] Methyl iodide reacts with $Pt(PEt_3)_3$ via oxidative addition, the process being overall of the second order. The interception of free radicals by radical traps, such as tert-BuNO', is indicative of the participation of radical intermediates.[28] A radical-chain process is proposed for such reactions involving a one-electron transfer step.[28]



$n = 2, 3$: RX = MeI, $MeCH_2I$: L = PPh_3. (15)

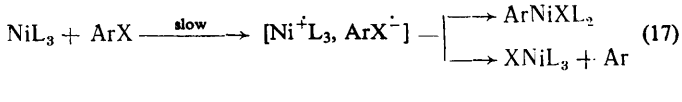
A mechanism involving an initial complex formation between halide and complex, $M(0)L_n$, is involved for reactions of unsaturated organic halides.[34]



(16)

Contrasting with nucleophilic aromatic substitution,[35] the reactivity of aryl halides decreases in the following order: I > Br > Cl. Electron-accepting substituents in the aromatic ring facilitate oxidative addition.[36]

Oxidative addition of aryl halides to zero-valent nickel complexes leads to the formation of a paramagnetic Ni(I) complex in addition to a *trans*-arylnickel(II) halide.[37,38] The proportion of each depends on the nature of the halogen in ArX, the type of ring substituent, and the solvent. The reaction is overall of the second order. It is proposed that the rate-determining stage is the one-electron oxidation of the Ni(0) complex with the aryl halide; the radical-ion pair thus formed reacts by two independent pathways affording the product of oxidative addition and an Ni(I) complex. It is possible that the electron transfer step precedes π-complex formation between the reactants.

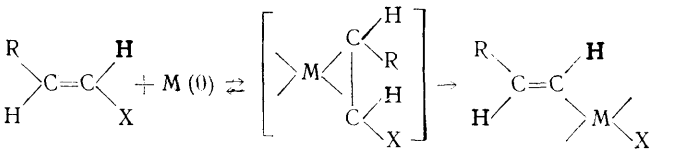


(17)

It should be pointed out that Ni(I) complexes may react with aryl halides with the formation of arylnickel(III) complexes; however, this reaction proceeds far more slowly than the reaction of ArX with an Ni(0) complex. According to one report,[38] oxidative addition to Ni(I) is the key step in the synthesis of biaryls from aryl halides in the presence of nickel complexes and metallic zinc.

$$Ni^{I}X + ArX \rightarrow ArNi^{III}X_2,$$
$$ArNi^{III}X_2 + ArNi^{II}X \rightarrow Ar_2Ni^{III}X + NiX_2,$$
$$Ar_2Ni^{III}X \rightarrow Ar{-}Ar + Ni^{I}X. \quad (18)$$

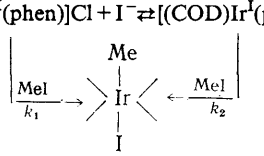
The reaction of vinyl halides with Pt-, Pd-, and Ni-complexes takes place with retention of the (*E*) or (*Z*)-configuration of the unsaturation, leading to the corresponding σ-vinylmetal complex.[39–44] It is proposed[44] that oxidative addition precedes formation of a π-olefin complex. Such a complex has, in fact, been isolated, and characterised, from the reaction of perhalogenoethylenes with Pt(0).[45]


(19)

It is unlikely that oxidative addition of vinyl halides proceeds via formation of free radicals as vinyl radicals readily undergo configurational isomerisation.[46]

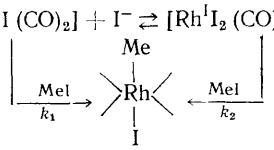
There are several examples of anionic catalysis in oxidative addition.[47–49] The coordination of anions, such as iodide ion, leads to the formation of anionic complexes which display significantly higher activity than the corresponding uncharged complexes in oxidative addition. Of the two examples shown below, the second provides the basis of the industrial synthesis of acetic acid (Monsanto).

$$[(COD)Ir^{I}(phen)]Cl + I^- \rightleftarrows [(COD)Ir^{I}(phen)I]^-$$


(20)

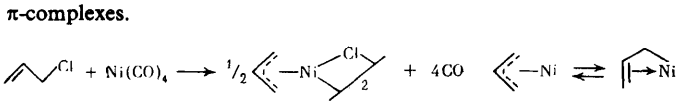
$$k_2 \simeq 7k_1$$

$$[Rh^{I}I(CO)_2] + I^- \rightleftarrows [Rh^{I}I_2(CO)_2]^-$$

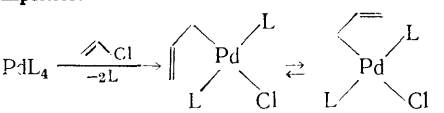

(21)

$$k_2 > k_1$$

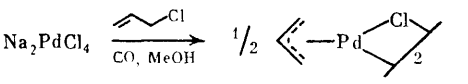
Allyl halides are more active than alkyl, vinyl or aryl halides in oxidative addition. They readily react with nickel, palladium and platinum complexes even in the absence of strong donor ligands. Thus, nickel tetracarbonyl interacts with allyl halides to produce dimeric π-allyl complexes.[50] According to PMR data, a mobile equilibrium is established between the corresponding σ- and π-complexes.

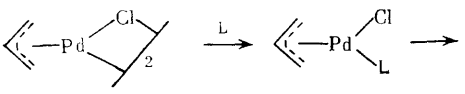

(22)

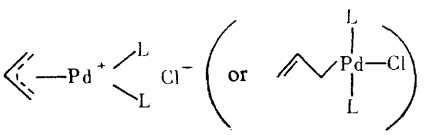
The reaction of allyl chlorides with tetrakis(triphenylphosphine)-palladium(0) leads to the formation of an equilibrium mixture of allyl complexes.[51]


(23)

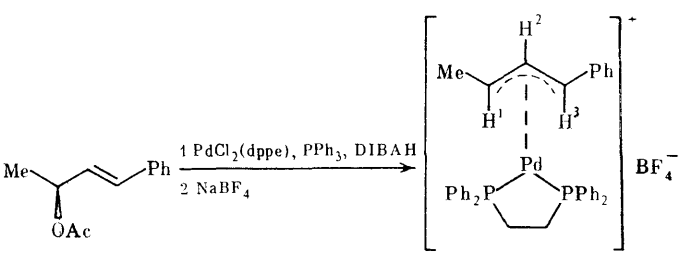
Palladium(0), generated by reduction of Pd(II) salts, interacts with allyl chlorides to give the corresponding bis(π-allylpalladium chlorides).[52] Treatment of the latter with excess of phosphine affords either a cationic π-allyl complex or a σ-complex, depending on the nature of the solvent.[51]


(24)



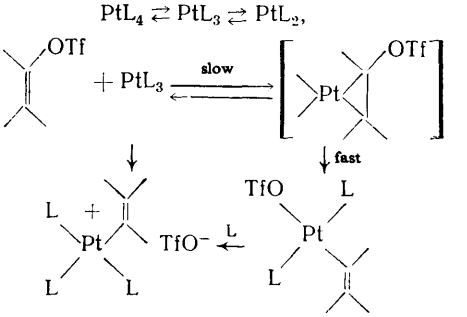

(25)

Oxidative addition of allylic substrates to zero-valent palladium complexes proceeds with inversion of configuration.[53]

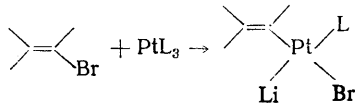

(+)-(1*R*, 2*S*, 3*S*) (26)

Substrates having a leaving group other than halogen may also participate in oxidative addition; however, such reactions have been studied relatively little. There are, however, a large number of catalytic reactions of organometallic compounds with organic triflates,[54] phosphates,[55] with simple and allylic silyl enol ethers,[56,57] and sulphides,[58] tellurides,[59] and with selenides.[60] The mechanism of the reaction of vinyl triflates with zero-valent platinum complexes has been studied.[61] On the basis of a detailed product analysis, a study of the kinetics and stereochemistry of the reaction, a comparison of the reactivity of structurally diverse vinyl triflates, and an NMR study of intermediates, the mechanism of the reaction would appear to involve formation of a vinyl triflate π-complex with Pt(0).

$$PtL_4 \rightleftarrows PtL_3 \rightleftarrows PtL_2,$$

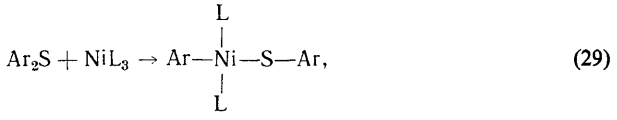

(27)

It should be pointed out that neutral complexes are obtained on reaction of vinyl bromides with PtL_3, rather than cationic complexes as are formed with vinyl triflates.



(28)

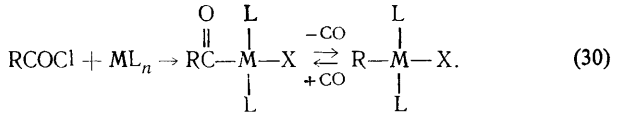
The interaction of diaryl sulphides with tris(tri-n-butylphosphine)-nickel leads to products of oxidative addition across the carbon–sulphur bond, as evident from NMR data and X-ray structural analysis.[62]



(29)

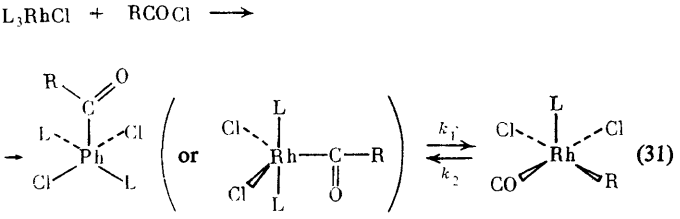
Ar = *p*-$MeOC_6H_4$, C_6F_5; L = n-Bu_3P.

Acyl chlorides also take part in oxidative addition with zero-valent nickel, palladium and platinum complexes.[63,64] Subsequent decarbonylation takes place most easily with nickel complexes.



(30)

Depending on the structure of the acyl group, reaction of acyl chlorides with Rh(I) complexes yields square-pyramidal or trigonal-bipyramidal complexes.



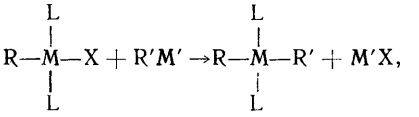
(31)

Rearrangement of acyl to carbonyl complexes proceeds reversibly ($k_1/k_{-1} = 7\times10^{-2}$) where R = $C_6H_5CH_2$, and irreversibly where R = Ar.[65,66]

The d^8 complexes of the nickel triad formed by oxidative addition may react further with organic halides to produce the corresponding d^6 complexes. There are many examples where such complexes are formed with Pr(II),[67] and complexes of the type *fac*-L_2PtIMe_3 have been isolated and characterised. A Pd(IV) complex with three σ-bonded methyl groups, *fac*-[$PdMe_3$(2,2′-bipyridyl)I], has also been prepared for the first time and characterised structurally.[68]

III. Transmetallation

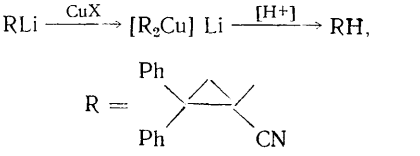
Transmetallation is the next step of the catalytic cycle in the cross-coupling of organometallic compounds with organic halides. In the process the halogen atom in the complex $RMXL_2$ is replaced by the organic residue, R′, of the organometallic compound



(32)

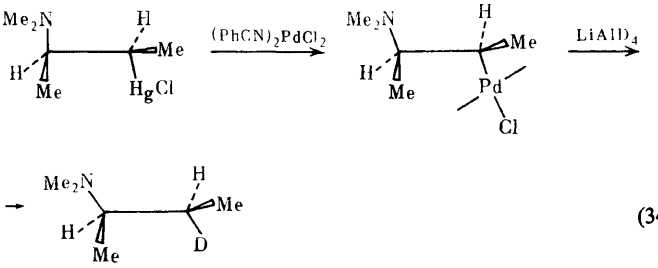
M = Ni, Pd; M′ = Li, Mg, Zn etc.

Transition metal complexes with σ-bonded organic residues may be generally prepared via transmetallation. It involves the interaction of a transition metal halide with an organometallic compound of a non-transition element to produce a transition metal compound with one or more σ-bonded organic groups.[21] The detailed mechanism by which the organic residue of the organometallic compound is transferred to the transition metal has not, as yet, been established; however, in a number of cases, it has been shown that this process takes place stereospecifically. Thus, the cyclopropyl group of lithiated cyclopropanes is transferred to copper with retention of configuration.[69]



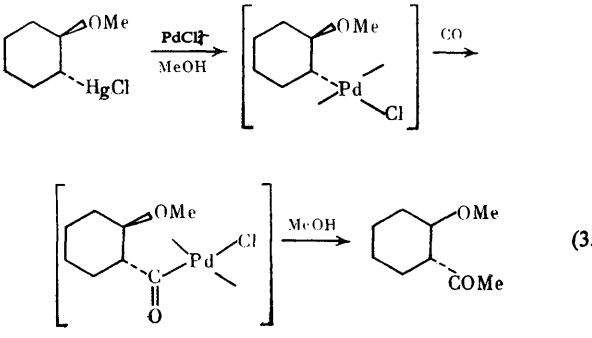
(33)

Organomercury compounds are widely used for the preparation of transition metal complexes.[70] Mechanistically, the reaction involves electrophilic cleavage of the mercury–carbon bond with the transition metal halide. The alkyl group of the organomercury compound transfers to Pd(II) with retention of configuration, as shown in the reactions of the *erytho*- and *threo*-isomers of β-amino-ethylmercury chlorides with bis(acetonitrile)dichloropalladium(II).[71]



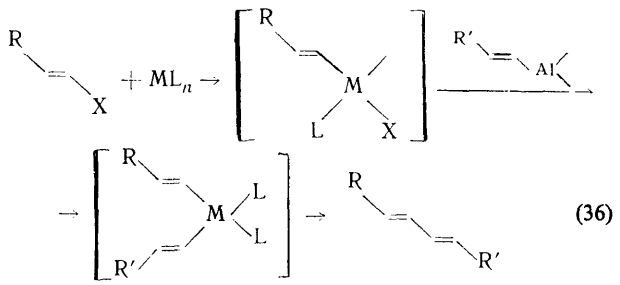
(34)

Retention of configuration on transmetallation is also observed with cyclohexylmercury compounds.[72]



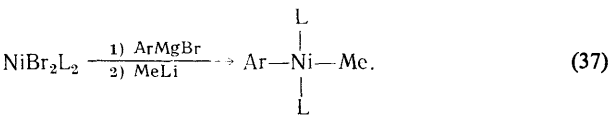
(35)

The configuration at the sp^2 carbon atom is retained at all stages of the catalytic cycle, as illustrated in the reactions of vinylalanes with vinyl halides catalysed by nickel and palladium complexes.[73]



(36)

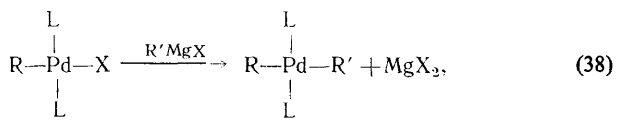
Nickel(II) complexes with two σ-bonded organic groups have also been obtained by transmetallation.[74]



(37)

L = PEt_3

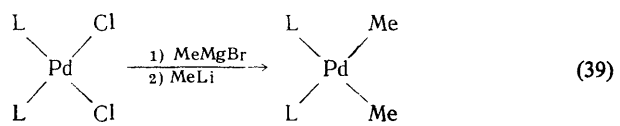
The *trans*-configuration of the nickel complexes has been confirmed by a ^{31}P NMR study.[74] Complexes of the type, *trans*-$RPdR'L_2$, have been isolated by reaction of Grignard compounds with $RPdXL_2$ complexes obtained by oxidative addition of RX to Pd(0).[19,75]



(38)

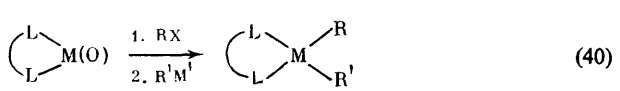
L = PEt_2Ph, PEt_3.

The corresponding *cis*-palladium complexes have been prepared from *cis*-$PdCl_2L_2$ by sequential transmetallation with organomagnesium and -lithium compounds.[76]



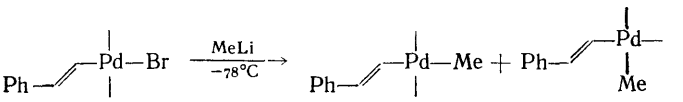
(39)

Nickel and palladium complexes with bidentate, configurationally locked, ligands may react sequentially with organic halides and organometallic compounds with the formation of the corresponding *cis*-diorgano-complexes.



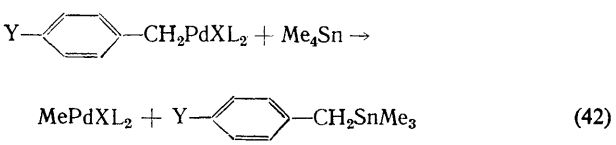
(40)

By a ^{31}P NMR study,[77] it has been shown that transmetallation of palladium *trans*-(*E* or *Z*)-styryl complexes with methyllithium leads to a mixture of *trans*- and *cis*-methyl(styryl)palladium complexes.



(41)

The interaction of benzylpalladium(II) complexes with tetramethyltin in HMPA at 25 °C results in exchange of the benzyl group by methyl, rather than exchange of a halogen atom on the metal.[78]



(42)

The interaction of organolithium compounds with L_2PdCl_2 complexes leads to tri- and tetra-organopalladates.[79] The resistance of the latter to reductive elimination (see below) is evidently the reason why lithium acetylides are inert towards cross-coupling.[15]

IV. Reductive elimination

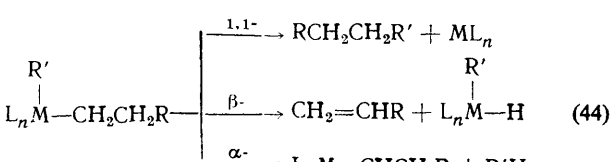
Reductive elimination, the reverse of oxidative addition, proceeds with formation of a bond between ligands X and Y and reduction of the coordinated metal. This type of conversion is particularly important because it results in the liberation of the desired organic product in the final step of the catalytic cycle of the cross-coupling. The same process is involved in the majority of other homogeneous catalytic reactions.



(43)

In an earlier review,[80] the basic features of reductive elimination, namely the associated formation of carbon–carbon, carbon–hydrogen and carbon–heteroatom bonds, have been outlined. Here we shall focus primarily on that process by which the carbon–carbon bond is formed.

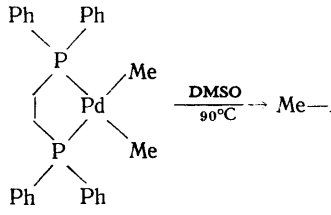
β-Elimination is notably prevalent with transition metal alkyl complexes. If this elimination is not possible (where, for example, there is no β-hydrogen atom, or where a free coordination site on the metal complex is not available, etc.), the complex undergoes α-elimination or 1,1-reductive elimination.



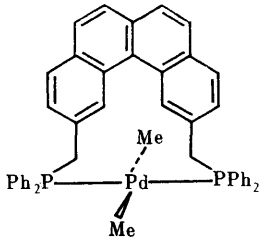
(44)

1,1-Reductive elimination of two organic residues with subsequent formation of a new carbon–carbon bond is the key step in catalytic cross-coupling. Before reductive elimination takes place, the ligands must be *cis*-oriented. As seen in the examples below, ethane is

readily eliminated from two *cis*-oriented methyl ligands, while *trans*-oriented groups fail to react.[76]



$$\xrightarrow[90^\circ C]{DMSO} Me{-}Me \qquad (45)$$



$$\xrightarrow[100^\circ C]{DMSO} \text{no reaction} \qquad (46)$$

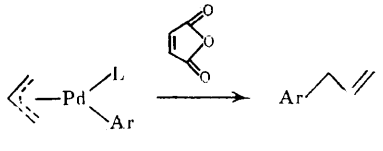
The rate of reductive elimination is increased if there is a positive charge on the complex. Thus, the Pt(IV) complex, $PtL_2Ph_2I_2$, is stable in benzene but readily eliminates iodobenzene in methanol. Evidently, the cationic complex formed by dissociation of iodide ion eliminates iodobenzene far more readily than the corresponding neutral complex.[81]

$$\begin{array}{ccc} PtL_2Ph_2I_2 & \overset{MeOH}{\rightleftharpoons} & [PtL_2Ph_2I\,(MeOH)]^+I^- \\ \downarrow PhH & & \downarrow -PhI \\ \text{no reaction} & & [PtL_2Ph\,(MeOH)]^+I^- \\ & & \downarrow \\ L = PEt_3 & & PtL_2PhI \end{array} \qquad (47)$$

An oxidant may be employed to initiate reductive elimination. It has been shown, for example, that ethylene and ethane are isolated as the initial elimination product by thermolysis of the neutral complex, $Et_2Fe(bipy)_2$;[82] however, rapid and selective formation of butane can be achieved by 2-electron oxidation of the complex by electrochemical means or on treatment with $[IrCl_6]^{2-}$.

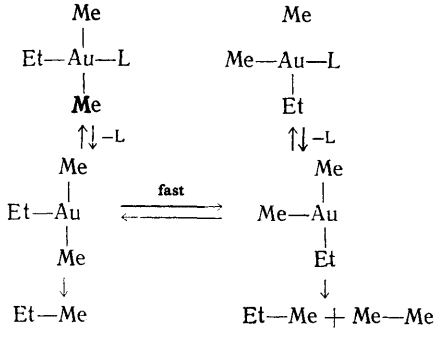
$$Et_2Fe\,(bipy)_2 \xrightarrow{-2e^-} n\text{-}C_4H_{10}. \qquad (48)$$

Even the formation of charge-transfer complexes with electron-deficient olefins may initiate elimination of alkane from dialkyl complexes of the type $Et_2Ni(bipy)$.[83] Thus, olefins such as maleic anhydride and tetracyanoethylene induce reductive elimination from palladium π-allyl complexes with formation of coupling products of the type allyl–allyl and allyl–aryl.[84,85]



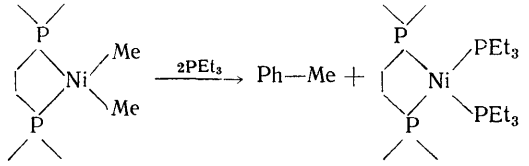
(49)

The accelerating effect of the positive charge does not require any further explanation since reductive elimination is, in itself, a process involving oxidation by the metal atom—in this case oxidation of two organic ligands. In the process by which the ligands (even the neutral ones) are dissociated, there is an increase in the actual positive charge on the metallic centre, and the rate of reductive elimination increases. Planar gold complexes of the type R_3AuL undergo reductive elimination through formation of tri-coordinate *T*-shaped intermediates. Because *cis*- and *trans*-$EtMe_2AuL$ afford a mixture of ethane and propane in equal amount, it follows that *T*-shaped complexes isomerise more readily than undergo elimination of R–R.[86]

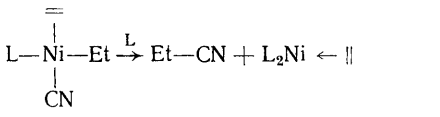


(50)

However, some reductive eliminations do not require preliminary dissociation of the ligand. Examples are known wherein elimination is enhanced if coordination of another ligand takes place.[87,88]



(51)



(52)

According to one report,[74] two concurrent processes are involved in the reductive elimination of planar nickel complexes of the type $ArNiMe(PEt_3)_2$. A dissociative mechanism is at play during thermolysis of the complex, by which a preliminary cleavage of the ligand takes place.

$$ArNiMeL_2 \rightleftarrows ArNiMeL + L,$$

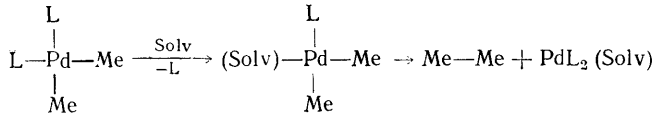
$$ArNiMeL \rightarrow Ar{-}Me + NiL. \qquad (53)$$

Aryl halides induce the second step which involves a radical-chain process with the participation of paramagnetic Ni(I) and Ni(III) species. The radical character of this step is indicated by the formation of radical products, by an induction period, and by the strong influence of promoters and inhibitors on the reaction rate.

$$\left.\begin{array}{l} ArNiMe \xrightarrow{\Delta} ArMe + Ni^0, \\ ArX + Ni^0 \rightarrow Ar^{\cdot} + Ni^{I}X, \\ Ar^{\cdot} + Ni^0 \rightarrow ArNi^{I}, \end{array}\right\} \text{initiation}$$

$$\left.\begin{array}{l} ArNi^{I} + ArX \rightarrow Ar_2Ni^{III}X, \\ Ar_2Ni^{III}X + ArNi^{II}Me \rightarrow ArNi^{II}X + Ar_2Ni^{III}Me, \\ Ar_2Ni^{III}Me \rightarrow ArMe + ArNi^{I} \text{ etc.} \end{array}\right\} \text{chain extension} \qquad (54)$$

The key characteristics of reductive elimination have been studied in detail with palladium complexes, R_2PdL_2. Thus, it has been established that elimination of ethane from *cis*-Me_2PdL_2 is a first-order reaction involving a dissociative mechanism.[89]

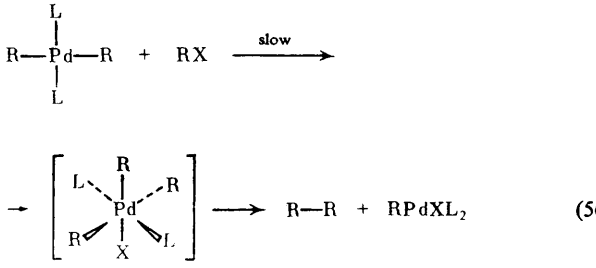


Solv – solvent

(55)

This mechanism is in accord with theoretical calculations for the reductive elimination of ethane from bis(phosphine)dimethylpalladium complexes.[90] The main conclusions drawn from these calculations are the following. Strong donor ligands *trans* to a methyl group hinder elimination. Reductive elimination of ethane from 4-coordinate complexes, *cis*-Me_2PdL_2, is allowed by symmetry, and determined by the energy of the antisymmetrical b_2 orbital of the palladium complex. The value of the energy barrier for elimination from palladium complexes is far higher than the corresponding value for nickel complexes in which the energy of the b_2-orbital is lower. The activation energy for elimination of ethane from 3-coordinate *T*- and *Y*-shaped intermediates is less than that for complexes Me_2PdL_2. The energy barrier for isomerisation from one *T*-structure to another is significantly greater than the barrier for elimination from *T*- and *Y*-shaped complexes (compare reductive elimination of R–R from R_3AuL [50]).

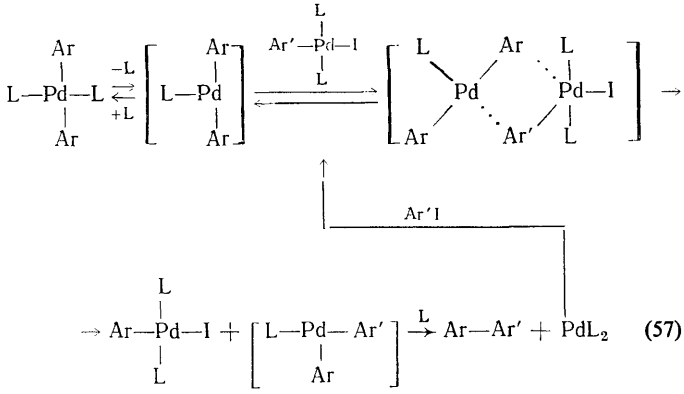
The foregoing explains why *trans*-R_2PdL_2 complexes, which routinely participate in catalytic cross-coupling, must initially isomerise into *cis*-R_2PdL_2. A coordinating solvent (THF, DMSO, DMF) of an additional phosphine ligand is required for isomerisation, i.e. *trans-cis* isomerisation takes place by an associative mechanism.[76] If *trans-cis* isomerisation is not possible for steric reasons, then the complexes resist reductive elimination.[46] Yet *trans*-Me_2PdL_2 complexes do react with CD_3I, even at 20 °C, to give 1,1,1-trideuterioethane exclusively.[76] Added CH_3I also increases the rate of formation of ethane from *cis*-dimethylpalladium complexes.[89] According to certain authors,[89] these data confirm that reductive elimination from R_2PdL_2 in the presence of organic halide proceeds through intermediate formation of palladium(IV) intermediates.



(56)

There is, in fact, one report on the isolation and full characterisation of a Pd(IV) complex, *fac*-$Me_3PdI(bipy)$.[68] The possible participation of Pd(IV) intermediates has been critically evaluated.[91]

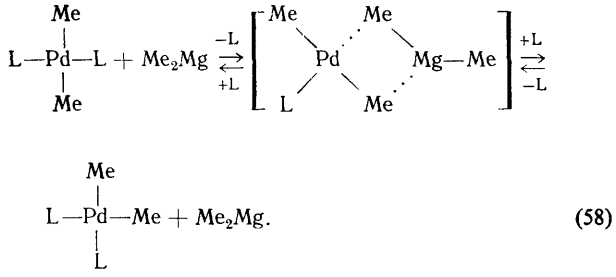
According to another report,[92] the rate of reductive elimination of biaryls from *trans*-Ar_2PdL_2 in the presence of aryl iodide is not dependent on the intermediate formation of a Pd(IV) complex, but rather on the facile isomerisation of *trans*-Ar_2PdL_2 into the *cis*-complex under the influence of *trans*-$Ar'PdIL_2$, obtained by oxidative addition of Ar'I to the Pd(0) complex.



(57)

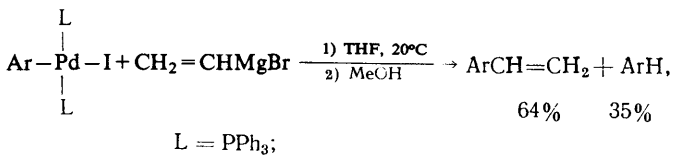
The catalysed isomerisation of Ar_2PdL_2 by $Ar'PdIL_2$ is accompanied by a profound reorganisation of organic residues, leading to the formation of three types of biaryl: ArAr', Ar_2 and Ar'_2.[92]

However, under the conditions for catalytic cross-coupling with organomagnesium compounds ($RX:R'MgX:PdL_n$ = 1:1.5:0.01), the process shown in Eqn. (57) is unlikely because $RPdXL_2$ complexes readily react with R'MgX to give $RPdR'L_2$. At the same time, it has been shown that *trans-cis* isomerisation proceeds readily on treatment with organomagnesium compounds.[79]



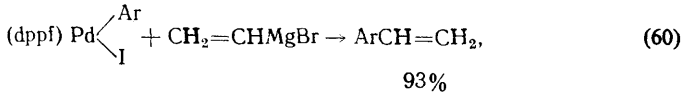
(58)

In this context, it is unlikely that *cis-trans* isomerisation would take place in the presence of organomagnesium compounds under the conditions of the actual catalytic cycle of the cross-coupling between RX and R'MgX. The following data (schemes 59 and 60), taken from a product analysis[93] of the reaction of *trans*-$ArPdIL_2$ and *cis*-ArPdI(dppf) [where dppf is 1,1'-bis(diphenylphosphino)-ferrocene] with vinylmagnesium bromide ($ArPdIL_2:CH_2=CHMgBr$ = 1:100), support this contention.



L = PPh_3;

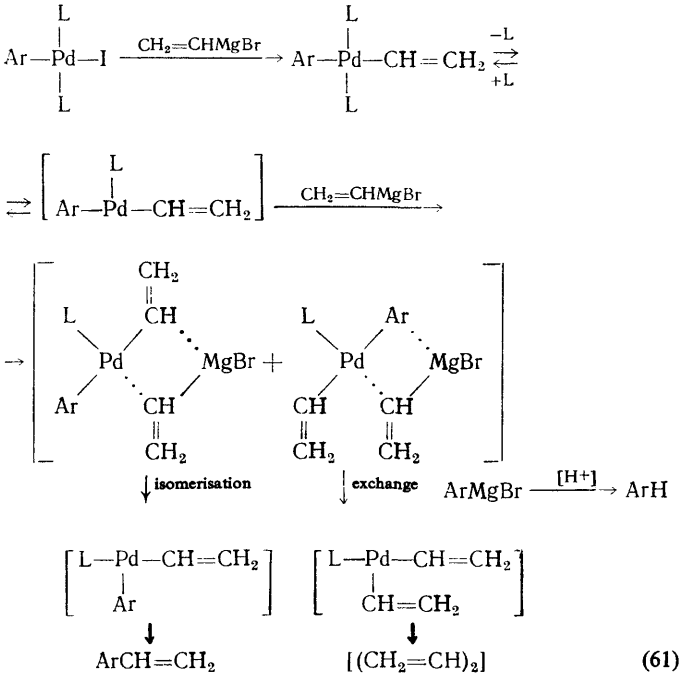
(59)



Ar = *p*-PhC_6H_4.

(60)

It should be pointed out that the corresponding catalysed reaction of *p*-iodobiphenyl with $CH_2=CHMgBr$ leads to the same type of products. The results are summarised in scheme (61). Here, the interaction of a *trans-T*-type intermediate, $ArPd(CH=CH_2)L$, with vinylmagnesium bromide is critical. This takes place by two independent routes: via *trans-cis* isomerisation and via exchange of organic residues beteween the organopalladium and organomagnesium compounds.



(61)

If the *trans-cis* isomerisation had taken place with the participation of the complex $ArPdIL_2$, then the tetraphenyl *p*-quaterphenyl would have been present in the reaction product.[59]

The absence of side-products from reactions involving palladium complexes with bidentate ligands, by which mono- and diorganocomplexes are formed with the *cis*-configuration, would suggest that transmetallation and subsequent reductive elimination take place in such cases far more readily than the exchange process.

V. The influence of the ligand environment in the transition metal complex on the efficiency of cross-coupling

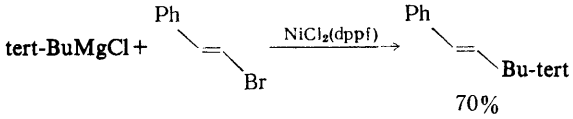
The correct choice of ligand for the nickel of palladium complexes is critical for the cross-coupling to succeed. A comparison has been made of various nickel complexes as catalysts for the reaction of chlorobenzene with n-butylmagnesium bromide.[94]

$$PhCl + n\text{-}BuMgBr \xrightarrow{NiCl_2L_2} n\text{-}Bu-Ph \quad 81-100\% \qquad (62)$$

L_2 = dppp[1,3-bis(diphenylphosphino)propane], dmpf[1,1′-bis(dimethylphosphino)ferrocene].

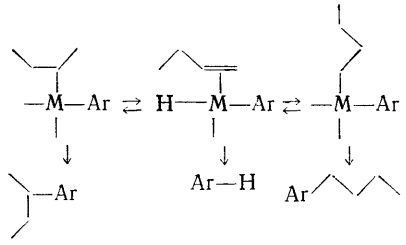
Nickel complexes with other phosphine ligands have little catalytic activity.[62] Generally speaking the choice of ligand is governed by the structure of the organic residue in RX and R′MgX.[94]

For cross-coupling of n-, *sec*- and tert-alkylmagnesium halides with aryl and vinyl halides, it has been shown that nickel and palladium catalysts with the bidentate ligand, 1,1′-bis(diphenylphosphino)ferrocene (dppf), are selective and afford the desired products in high yield.[95,96]



(63)

The correct choice of ligand is especially important in the alkylation of aryl halides where isomerisation of *sec*-alkyl groups and reduction of ArX to ArH could complicate the desired cross-coupling. The mechanism of these side reactions, i.e. isomerisation and reduction, has been examined [97] (see scheme 64).



(64)

The absence of side-products when dppf is used as ligand confirms that, in this case, reductive elimination with the formation of *sec*-BuAr proceeds significantly more rapidly than β-elimination.

Thus selectivity and catalytic activity of palladium complexes with bidentate bis(diphenylphosphino) ligands depends on the distance between the two diphenylphosphino groups.[98] For alkylation in the presence of bis(diphenylphosphino)palladium complexes, selectivity increases as the P—Pd—P bond angle increases in the sequence dppe < dppp < dppf, and as the Cl—Pd—Cl bond angle decreases in the sequence dppe > dppp > dppf. As is the case with *cis*-(*sec*-Bu)$PdArL_2$ complexes, the increase in selectivity (in the order dppe < dppp < dppf) is, in all likelihood, associated with the increased rate of reductive elimination, determined by the more facile approach of the organic residues.

It has been shown that nickel complexes with bi- and tetra-dentate ligands (β-diketones, β-ketothiones, β-ketoimines, amino-acids, diamines, etc.) exert a high catalytic activity in the reactions of aryl-Grignard compounds with aryl halides.[99]

$$PhMgBr + o\text{-}PhC_6H_4I \xrightarrow{«Ni»} o\text{-}PhC_6H_4Ph \quad \text{up to } 90\% \qquad (65)$$

Recently, $PdCl_2$(dppf) was shown to have high catalytic activity in the reactions of alkylboron compounds with aryl and alkenyl halides.[100]

In conclusion, it should be pointed out that, of all the catalysts used at the present time in cross-coupling, $PdCl_2$(dppf) is the most versatile by virtue of its high activity and selectivity.

References

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