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Mechanisms of the Mizoroki–Heck Reaction

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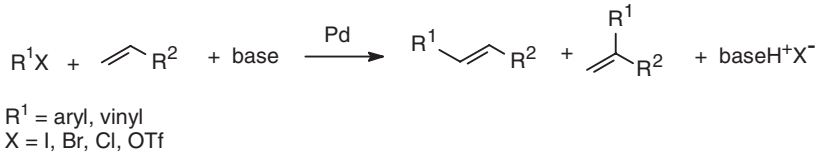
1.1 Introduction

The palladium-catalysed Mizoroki–Heck reaction is the most efficient route for the vinylation of aryl/vinyl halides or triflates. This reaction, in which a C—C bond is formed, proceeds in the presence of a base (Scheme 1.1) [1, 2]. Nonconjugated alkenes are formed in reactions involving cyclic alkenes (Scheme 1.2) [1e, 2a,c,e,g] or in intramolecular reactions (Scheme 1.3) [2b,d–g] with creation of stereogenic centres. Asymmetric Mizoroki–Heck reactions may be performed in the presence of a chiral ligand [2]. The Mizoroki–Heck reaction has been intensively developed from a synthetic and mechanistic point of view, as expressed by the impressive number of reviews and book chapters [1, 2].

In the late 1960s, Heck reported that arylated alkenes were formed in the reaction of alkenes with a stoichiometric amount of [Ar–Pd—Cl] or [Ar–Pd–OAc], generated *in situ* by reacting ArHgCl with $PdCl_2$ or ArHgOAc with $Pd(OAc)_2$ respectively [3]. A mechanism was proposed which involves a *syn* migratory insertion of the alkene into the Ar–Pd bond, followed by a *syn* β-hydride elimination of a hydridopalladium [HPdX] (X = Cl, OAc) (Scheme 1.4a). In the case of cyclic alkenes, in which no *syn* β-hydride is available, a *syn* β'-hydride elimination occurs, leading to a nonconjugated alkene (Scheme 1.4b). Isomerization of the new C=C bond may occur by a *syn* readdition of HPdX in the reverse direction, followed by a *syn* β''-hydride elimination (Scheme 1.4c) [3c].

The Mizoroki–Heck Reaction Edited by Martin Oestreich



Scheme 1.1

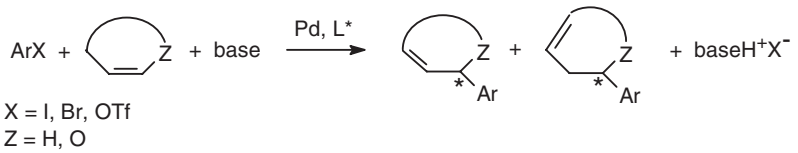
These pioneering studies by Heck have opened the way to a new reaction later called the Mizoroki–Heck reaction (Scheme 1.1). In 1971, Mizoroki *et al*. reported preliminary results on the $PdCl_2$-catalysed arylation of alkenes by iodobenzene in the presence of potassium acetate as base (Scheme 1.5) [4]. No new contribution to the mechanism was proposed, except that palladium particles, formed *in situ* in the reaction or deliberately added, were suggested to be the active catalyst [4].

In 1972, Heck and Nolley [5] improved the reactions by using $Pd(OAc)_2$ as catalyst and n-Bu_3N as base (Scheme 1.6). The reactions were performed without any solvent or in *N*-methylpyrrolidone (NMP) at 100 °C. More importantly, they proposed for the first time a full mechanism for the catalytic reactions. On the basis of what were at that time recent studies by Fitton and coworkers and Coulson on the formation of σ-$ArPdXL_2$ ($L = PPh_3$; X = I [6a,c], Br [6c], Cl [6b]) by oxidative addition of aryl halides to Pd^0L_4, Heck and Nolley proposed the formation of [ArPdI] in the oxidative addition of aryl iodide to palladium metal, generated *in situ* by reduction of $Pd(OAc)_2$ by the alkene. After reaction of [ArPdI] with the alkene as in Scheme 1.4a, the hydridopalladium [HPdI] decomposes to HI (quenched by the base) and palladium(0) available for another catalytic cycle [5].

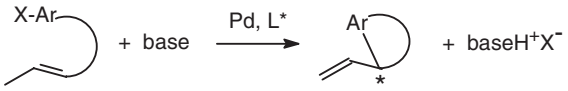
In 1973, Mizoroki and coworkers [7] extended their preliminary work (Scheme 1.5) to aryl bromides; however, these were found to be considerably less reactive than aryl iodides: PhI > PhBr ≫ PhCl. Palladium black was identified to be more efficient than $PdCl_2$. The use of a phosphine ligand PPh_3 was mentioned as being slightly beneficial [7]. This was the last contribution of the Japanese group to those reactions.

In 1974, Dieck and Heck [8] developed the use of PPh_3 in association with $Pd(OAc)_2$ (Scheme 1.7). Aryl iodides were found to react faster than without PPh_3. More interestingly, the reaction was extended to aryl bromides at temperatures in the range 100–135 °C, but aryl chlorides were still unreactive [8].

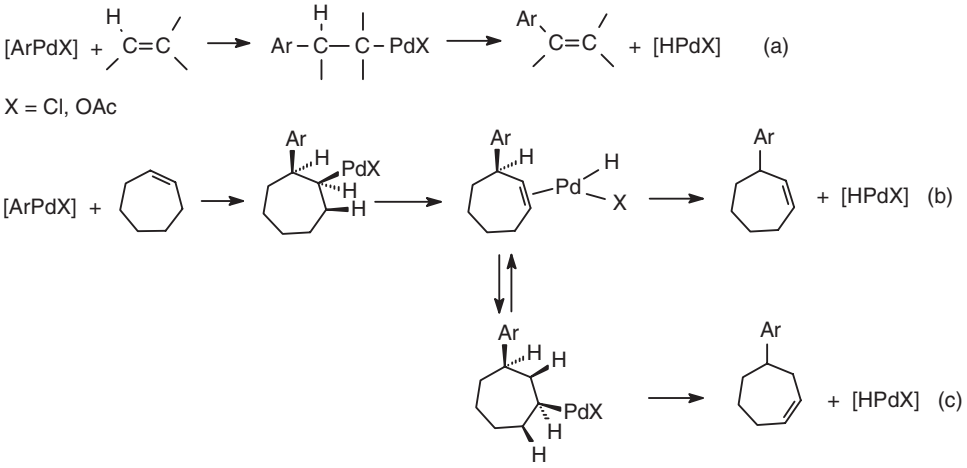
In 1978, Heck and coworkers [1a, 9] introduced substituted triarylphosphines associated with $Pd(OAc)_2$. Among them, the tri-*o*-tolylphosphine, $P(o\text{-Tol})_3$, was found to be more efficient than PPh_3 in reactions involving aryl bromides (experimental conditions of Scheme 1.7 at 75 °C). In 1983, Spencer improved the Mizoroki–Heck reactions catalysed by $Pd(OAc)_2$ associated with $P(o\text{-Tol})_3$ upon using the polar solvent DMF and NaOAc as



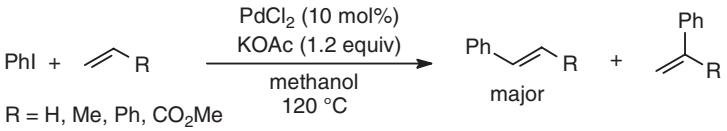
Scheme 1.2



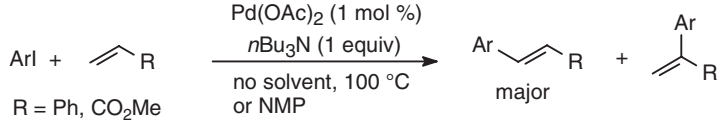
Scheme 1.3



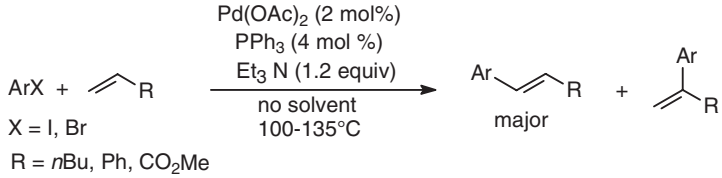
Scheme 1.4



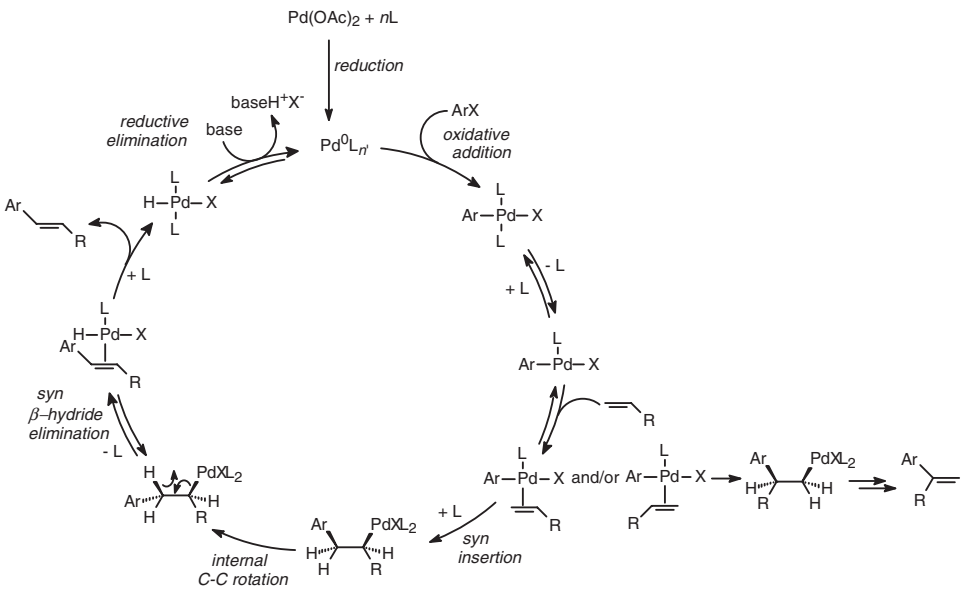
Scheme 1.5



Scheme 1.6



Scheme 1.7



Scheme 1.8 *Mechanism proposed by Heck when the precursor is $Pd(OAc)_2$ associated with monophosphine ligands L.*

base [10a]. High turnover numbers (TONs) were thus achieved from aryl bromides (e.g. TON = 134 000 in the reaction of *para*-nitrophenyl bromide and ethyl acrylate at 130 °C) [10a]. Surprisingly, PPh_3 associated with $Pd(OAc)_2$ was more efficient than P(*o*-Tol)$_3$ (P/Pd = 4 in both cases) for the reaction of electron-withdrawing group (EWG)-substituted aryl chlorides which, however, exhibited low reactivity (21–50% yield after 6 h at 150 °C). Chlorobenzene was rather unreactive (4% yield) [10b].

In 1974, a mechanism was proposed by Dieck and Heck [8] for reactions catalysed by $Pd(OAc)_2$ associated with monophosphine ligands. Such a mechanism written by Heck as successive reactions [1a–c] is presented as the catalytic cycle in Scheme 1.8. After formation of a Pd(0) catalyst from the precursor $Pd(OAc)_2$ by a vaguely defined reduction process, the following steps of the catalytic cycle were proposed:

(i) The first step of the catalytic cycle is an *oxidative addition* of the aryl halide to a Pd(0) complex. Such a step is supported by oxidative additions of aryl halides to $Pd^0(PPh_3)_4$ reported by Fitton and Rick [6c] in 1971 with the reactivity order: ArI > ArBr ≫ ArCl and *p*-EWG-ArX > *p*-EDG-ArX (EDG = electron-donating group).

(ii) The oxidative addition gives a σ-aryl–palladium(II) halide, *trans*-$ArPdXL_2$ [6c], which first coordinates to the alkene after dissociation of one phosphine and then undergoes a *syn insertion* of the alkene, leading to a σ-alkyl–palladium(II) halide. The phosphine dissociation step is supported by the fact that the reaction of *trans*-$PhPdBr(PPh_3)_2$ with ethylene is inhibited by extra phosphine [9]. The reaction of $ArPdXL_2$ with an alkene, also referred to as *carbopalladation* (formation of a Pd–C bond), is at the origin of the regioselectivity of Mizoroki–Heck reactions [8, 9]. Indeed, two isomeric σ-alkyl–palladium(II) halide complexes may be formed in an α or β

arylation of the alkene, leading to the branched or linear arylated alkene respectively (Scheme 1.8).

(iii) An internal C—C *bond rotation* in the σ-alkyl–palladium(II) halide brings an sp^3-bonded β-hydrogen in a *syn* position relative to the palladium atom. A *syn* β*-hydride elimination* gives a hydridopalladium(II) halide ligated to the arylated alkene. This reaction can be reversible (favoured in phosphine-free Mizoroki–Heck reactions), as proposed by Heck to explain some isomerization of the final arylated alkene by readdition of the hydridopalladium(II) halide onto its C=C bond with a reverse regioselectivity (see a similar process in Scheme 1.4b and c [8]).

(iv) After dissociation from the arylated alkene, the hydridopalladium(II) halide undergoes a reversible *reductive elimination* to regenerate the active Pd(0) complex. The base shifts this equilibrium towards the Pd(0) catalyst by quenching the hydrogen halide [9].

Under the same experimental conditions, same alkene, ligand and base, the reactivity order of aryl halides in Mizoroki–Heck reactions is usually: ArI > ArBr ≫ ArCl, suggesting that the *oxidative addition* is rate determining for the less reactive aryl halides. For the most reactive ones, the *complexation*/*insertion* of the alkene is considered as rate determining.

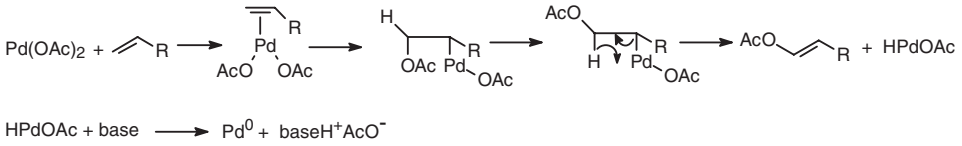
Besides the usual parameters of all reactions (temperature, solvent and concentration), other parameters may be varied (Pd precursors, ligands, bases, additives, etc.) to optimize Mizoroki–Heck reactions. Much work has been done in the last 30 years to perform Mizoroki–Heck reactions under mild conditions with high turnover numbers (TONs) [1v] and turnover frequencies (TOFs) [1, 2], to react aryl chlorides [1r,y], to improve the regioselectivity (α versus β arylation) [1e,g, 2g], to improve the enantioselectivity obtained with a chiral ligand when reacting cyclic alkenes [2a,c,e] or in intramolecular Mizoroki–Heck reactions [2b,d–f]. At the same time, the mechanism has been investigated to explain the high dependence of the efficiency and regioselectivity of Mizoroki–Heck reactions on the nature of the catalytic precursor, the base and the ligand.

It emerges that the main steps of the former textbook mechanism proposed by Heck have been confirmed (Scheme 1.8). However, the catalytic cycle may involve intermediate palladium complexes whose structures differ from those originally proposed, depending on the experimental conditions. One must also take into account the fact that new reagents (aryl triflates), new ligands (bidentate ligands, carbenes, bulky phosphines, etc.) and new precursors (palladacycles) have been introduced a long time after Heck's proposal.

The mechanisms of Mizoroki–Heck reactions performed from aryl derivatives are presented herein by highlighting how the catalytic precursors, the bases and the ligands may affect the structure and reactivity of intermediate palladium(0) or palladium(II) complexes in one or more steps of the catalytic cycle and, consequently, how they may affect the efficiency and regioselectivity of the catalytic reactions.

1.2 Mechanism of the Mizoroki–Heck Reaction when the Catalytic Precursor is $Pd(OAc)_2$ in the Absence of Ligand

As recalled in Section 1.1, $Pd(OAc)_2$ may be used as precursor without any phosphine ligand in Mizoroki–Heck reactions performed from aryl iodides [5]. However, $Pd(OAc)_2$

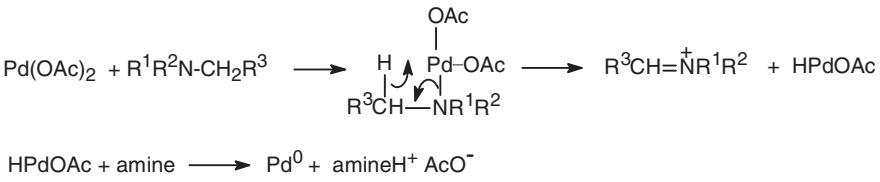


Scheme 1.9

must be reduced *in situ* to a Pd(0) species which initiates the catalytic cycle by an oxidative addition to the aryl iodide.

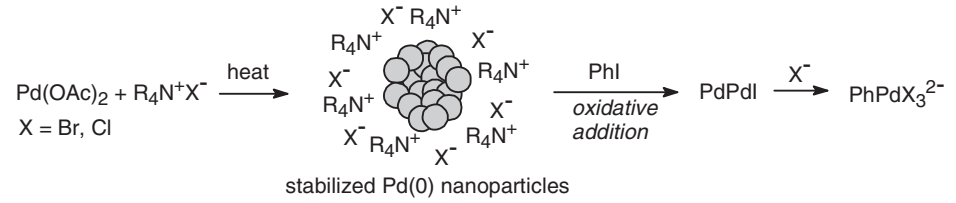
Some reagents of Mizoroki–Heck reactions may play the role of reducing agents, such as alkenes proposed by Heck [3b], according to the mechanism depicted in Scheme 1.9: intramolecular nucleophilic attack of acetate onto the alkene coordinated to $Pd(OAc)_2$, followed by a β-hydride elimination leading to HPdOAc and subsequent formation of Pd(0) in the presence of a base [3b, 11, 12].

Amines used as bases in Mizoroki–Heck reactions have also been proposed as reducing agents. Indeed, a β-hydride elimination may take place in the amine coordinated to the Pd(II) centre, leading to HPdOAc and then to Pd(0) in the presence of the amine (Scheme 1.10) [13].



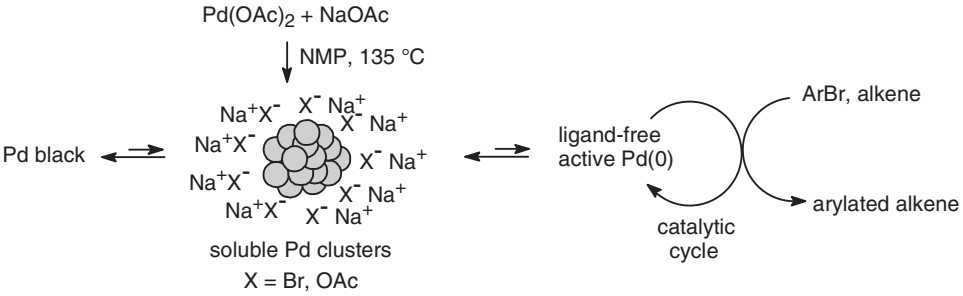
Scheme 1.10

Some additives, such as ammonium salts $R_4N^+X^-$ (X = Br, Cl, R = *n*-Bu), greatly improve Mizoroki–Heck reactions performed in the absence of phosphine ligands (Jeffery process [1h]). Reetz and Westermann [14a] have reported that thermolytic decomposition of $Pd(OAc)_2$ occurs at 100–130 °C in the presence of ammonium salts. The cleavage of the Pd–OAc bond generates $R_4N^+X^-$-stabilized Pd(0) nanoparticles (Scheme 1.11). Oxidative addition of PhI with those nanoparticles gives σ-bonded phenyl–Pd(II) species as PhPdI or $PhPdX_3^{2-}$ characterized by ^{1}H NMR spectroscopy (Scheme 1.11). Such Pd nanoparticles catalyse Mizoroki–Heck reactions [14]. Chlorobenzene can even react with styrene in the presence of $Pd(OAc)_2$ associated with the phosphonium salt $Ph_4P^+Cl^-$, yet at high temperatures (150 °C) in NMP [14b]. The homogeneous/heterogeneous character of the catalysis is under debate. De Vries *et al*. have developed so-called 'homeopathic' ligand-free Mizoroki–Heck reactions of aryl bromides and *n*-butyl acrylate, in the presence of low loading of $Pd(OAc)_2$ (0.05 mol%), NaOAc as base, in NMP at 130 °C [15a]. The lower the initial $Pd(OAc)_2$ concentration, the higher the TOF becomes. $Pd(OAc)_2$ is proposed to generate soluble clusters of palladium stabilized by Na^+X^- (X = AcO^- or/and Br^- in the course of the reaction) (Scheme 1.12). The latter inhibit the formation of inactive palladium black and deliver the active ligand-free Pd(0) into the catalytic cycle. Upon increasing $Pd(OAc)_2$ concentration, the two equilibria are shifted towards their



Scheme 1.11

left-hand sides, namely towards the formation of inactive palladium black. However, the 'homeopathic' ligand-free palladium does not catalyse Mizoroki–Heck reactions with aryl chlorides.



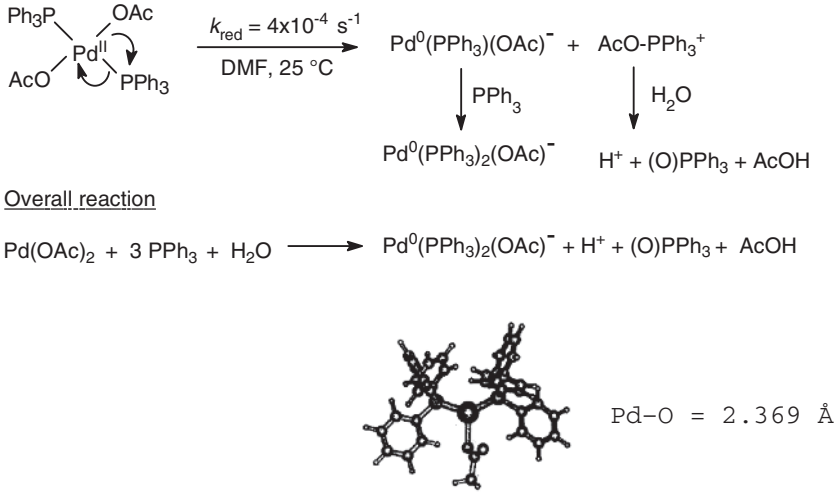
Scheme 1.12

Mechanistic investigations of Mizoroki–Heck reactions performed in the absence of stabilizing ligands are rare due to some difficulty in characterizing intermediate palladium species and getting kinetic data [16]. Nevertheless, de Vries *et al*. [15b] have characterized anionic species by electrospray ionisation mass spectrometry: H_2O–$Pd^0(OAc)^-$ and $PhPd^{II}I_2^-$, in a Mizoroki–Heck reaction performed from PhI, butyl acrylate, NEt_3 as base, $Pd(OAc)_2$ as catalyst in NMP at 80 °C. Anionic species $Pd^{II}{}_2I_6^{2-}$, $PhPd^{II}I_2^-$ and (η^2—CH_2═$C(CH_3)CH_2OH)PhPd^{II}I_2^-$ have been characterized by quick-scanning extended X-ray absorption fine structure in the course of a catalytic reaction (PhI, CH_2═$C(CH_3)CH_2OH$, NEt_3, $Pd(OAc)_2$, in NMP) [15c].

1.3 Mechanism of the Mizoroki–Heck Reaction when the Catalytic Precursor is $Pd(OAc)_2$ Associated with Monophosphine Ligands

1.3.1 Pd(0) Formation from $Pd(OAc)_2$ in the Presence of a Monophosphine Ligand

The catalytic precursor $Pd^{II}(OAc)_2$ associated with a monophosphine such as PPh_3 is more efficient than $Pd^0(PPh_3)_4$ in Mizoroki–Heck reactions. Two problems arise: (i) how an active Pd(0) complex can be generated from $Pd^{II}(OAc)_2$ associated with PPh_3; (ii) why the latter precursor is more efficient than $Pd^0(PPh_3)_4$, whereas both are supposed to generate the same reactive species $Pd^0(PPh_3)_2$ in the oxidative addition to aryl halides [17].



Scheme 1.13

In 1991, Jutand and coworkers discovered that a Pd(0) complex was generated *in situ* in tetrahydrofuran (THF) or dimethylformamide (DMF) at room temperature upon mixing $Pd(OAc)_2$ and *n* equivalents of PPh_3 ($n \geq 2$); that is, from the complex $Pd(OAc)_2(PPh_3)_2$ formed in the early stage [18]. In this process, PPh_3 is oxidized to the phosphine oxide, thereby attesting the reduction of Pd(II) to Pd(0) by the phosphine (Scheme 1.13) [18]. The rate of formation of the Pd(0) complex is not affected by the presence of alkene (decene) or amine (NEt_3) added in large excess to the initial mixture ($Pd(OAc)_2 + n$ equivalents of PPh_3 ($n \geq 2$)) [18]. Consequently, in the presence of a monophosphine ligand, the reduction of Pd(II) by the phosphine is much faster than that by the alkene or amine. Water does not modify the rate of formation of the Pd(0) complex [18]. The formation *in situ* of a Pd(0) complex from $Pd(OAc)_2$ and 5 equiv of PPh_3 in benzene in the presence of NEt_3 and water was confirmed shortly after by Osawa *et al*. [19].

Further studies by Amatore, Jutand *et al*. [20] on the kinetics of the reduction process have established that a Pd(0) complex is formed via an intramolecular reduction (reductive elimination) which takes place within the complex $Pd(OAc)_2(PPh_3)_2$ (first-order reaction for the palladium(II) and zero-order reaction for the phosphine) (Scheme 1.13). The rate constant of this rate-determining reduction process has been determined (k_{red} in Scheme 1.13). The reduction also delivers a phosphonium salt which is hydrolysed to phosphine oxide in a faster step (zero-order reaction for H_2O) (Scheme 1.13) [18].

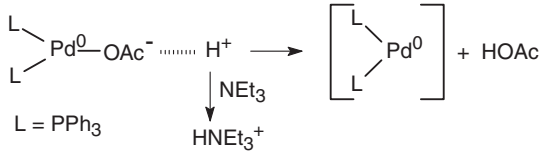
The formation of a Pd(0) complex by reduction of a Pd(II) complex by a phosphine is quite general. It takes place as soon as a Pd^{II}–OR (R = H, $COCH_3$, $COCF_3$) bond is formed. Pd(0) complexes are indeed generated from: (i) $PdCl_2(PPh_3)_2$ upon addition of a base OH^- (via $PdCl(OH)(PPh_3)_2$), as established by Grushin and Alper [21]; (ii) $PdCl_2(PPh_3)_2$ after addition of acetate ions (via $PdCl(OAc)(PPh_3)_2$) [22]; (iii) the cationic complex $[Pd^{II}(PPh_3)_2]^{2+}$,$2BF_4^-$ in the presence of water and PPh_3 (via $[Pd^{II}(OH)(H_2O)(PPh_3)_2]^+$) [23]; (iv) $Pd(OCOCF_3)_2 + nPPh_3$ [24].

The *in situ* formation of Pd(0) complexes takes place when $Pd(OAc)_2$ is associated with various phosphines: (i) aromatic phosphines $(p\text{-Z—}C_6H_4)_3P$ (Z = EDG or EWG). The formation of the Pd(0) complex follows a Hammett correlation with a positive slope [20]. The more electron-deficient the phosphine, the faster the reduction process; this is in agreement with the intramolecular nucleophilic attack of the acetate onto the ligated phosphine as proposed in Scheme 1.13; (ii) aliphatic phosphines [20]; (iii) water-soluble phosphines, triphenylphosphine trisulfonate (trisodium salt) [25] and triphenylphosphinetricarboxylate (trilithium salt) [26]. One major exception is the tri-*o*-tolylphosphine $P(o\text{-Tol})_3$, which cannot reduce $Pd(OAc)_2$ to a Pd(0) complex in DMF or THF. Instead, an activation of one C–H bond of the tolyl moieties by $Pd(OAc)_2$ takes place, leading to a dimeric *P*,*C*-palladacycle (see Section 1.5), as reported by Herrmann *et al*. in 1995 [27]. Such a Pd(II) *P*,*C*-palladacycle catalyses Mizoroki–Heck reactions [27]. It is, however, a reservoir of a Pd(0) complex, as recently established by d'Orlyé and Jutand [28] in 2005 (see Section 1.5).

The Pd(0) complex formed from $Pd(OAc)_2$ and 3 equiv PPh_3 is an anionic species $Pd^0(PPh_3)_2(OAc)^-$, where the Pd(0) is ligated by an acetate ion (Scheme 1.13) [29]. Further density functional theory (DFT) calculations by Shaik and coworkers [30] and Goossen *et al*. [31], support the formation of such anionic tri-coordinated Pd(0) complexes. The anionic 16-electron complex $Pd^0(PPh_3)_2(OAc)^-$ formed *in situ* from $Pd(OAc)_2$ and 3 equiv PPh_3 is, however, not that stable, yet it is more stable when generated in the presence of an amine (NEt_3) often used as a base in Mizoroki–Heck reactions. $Pd^0(PPh_3)_2(OAc)^-$ may indeed be destabilized by interaction of its acetate ligand with protons (generated in the hydrolysis of the phosphonium, Scheme 1.13) to give the unstable naked $Pd^0(PPh_3)_2$ complex. The capture of the protons by NEt_3 prevents this reaction and makes the anionic $Pd^0(PPh_3)_2(OAc)^-$ more stable (Scheme 1.14). This is the first unexpected role of the base [1k,m].

A Pd(0) complex is formed when 2 equiv of PPh_3 are added to $Pd(OAc)_2$. Since one PPh_3 is oxidized to $(O)PPh_3$, only one PPh_3 remains for the stabilization of the Pd(0) as in the formal complex $[Pd^0(PPh_3)(OAc)^-]$. The structure of the resulting Pd(0) complex must be more complicated, since two singlets of similar magnitude were observed in the ^{31}P NMR spectrum recorded in THF or DMF, suggesting the formation of *cis*- and *trans*-$[Pd^0(OAc)(\mu\text{-OAc})(PPh_3)]_2^{4-}$ [18]. These Pd(0) complexes are not stable; nevertheless, they react with iodobenzene, which explains why the catalytic precursor $\{Pd(OAc)_2 + 2PPh_3\}$ is efficient in Mizoroki–Heck reactions [8, 9]. Addition of more than 3 equiv of PPh_3 to $Pd(OAc)_2$ leads to the formation of the saturated stable (18-electron) $Pd^0(PPh_3)_3(OAc)^-$ which is in equilibrium with $Pd^0(PPh_3)_2(OAc)^-$ [29]:

$$Pd^0(PPh_3)_3(OAc)^- \rightleftarrows Pd^0(PPh_3)_2(OAc)^- + PPh_3$$

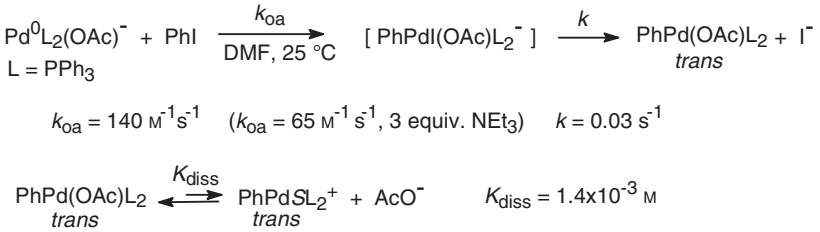


Scheme 1.14

1.3.2 Oxidative Addition

1.3.2.1 Oxidative Addition of Aryl Iodides

The 16-electron $Pd^0(PPh_3)_2(OAc)^-$ formed by reaction $Pd(OAc)_2$ and 3 equiv PPh_3 is found to be the only reactive species in the oxidative addition of iodobenzene [29]. It is more reactive than $Pd^0(PPh_3)_4$. Surprisingly, the expected *trans*-$PhPdI(PPh_3)_2$ is not produced in the oxidative addition; rather, a new complex *trans*-$PhPd(OAc)(PPh_3)_2$ is produced. The latter is in equilibrium with the cationic complex *trans*-$PhPdS(PPh_3)_2^+$ (S = DMF, THF) and AcO^- (Scheme 1.15) [18, 29, 32]. From the kinetics of the oxidative addition, it emerges that an intermediate complex is formed en route to *trans*-$PhPd(OAc)(PPh_3)_2$ in which the Pd(II) is still ligated by the iodide. Indeed, the kinetic curve for the release of iodide ions is S-shaped, proving that iodide is generated from an intermediate complex on the way to the final complex *trans*-$PhPd(OAc)(PPh_3)_2$ [18, 29]. The minimal structure for this intermediate was proposed as that of an anionic pentacoordinated complex $[PhPdI(OAc)(PPh_3)_2]^-$ (Scheme 1.15) [1m, 29, 33]. However, owing to its short life-time ($t_{1/2} = 30\,s$, DMF, 25 °C), this 18-electron complex does not play any role in the further step of Mizoroki–Heck reactions, being unable to be trapped by the slow reaction of the alkene before its evolution towards $PhPd(OAc)(PPh_3)_2$ [29].

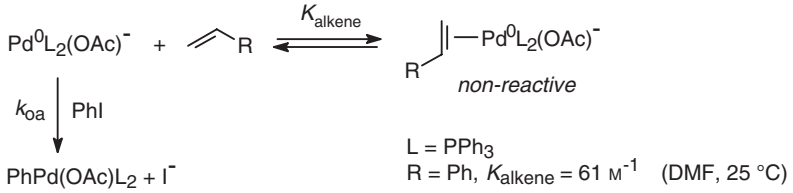


Scheme 1.15

Phosphine, Amines and Alkenes as Factors Affecting the Rate of the Oxidative Addition. Amatore, Jutand *et al.* [29] have established that excess PPh_3 slows down the oxidative addition by formation of the nonreactive $Pd^0(PPh_3)_3(OAc)^-$, thereby decreasing the concentration of the reactive $Pd^0(PPh_3)_2(OAc)^-$ by equilibrium with $Pd^0(PPh_3)_3(OAc)^-$.

The oxidative addition is also slower when performed in the presence of NEt_3, which stabilizes $Pd^0(PPh_3)_2(OAc)^-$ versus its decomposition by protons to the most reactive bent $Pd^0(PPh_3)_2$ (Scheme 1.14) [1m, 30]. This is the second unexpected role of the base: a decelerating effect on the oxidative addition.

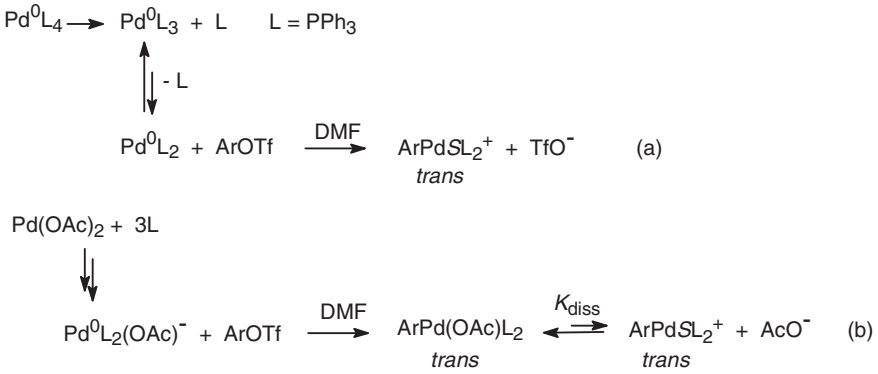
The oxidative addition is also slower when performed in the presence of an alkene, one of the components of the Mizoroki–Heck reaction. Owing to the reversible complexation of the reactive $Pd^0(PPh_3)_2(OAc)^-$ by the alkene which generates the nonreactive complex $(\eta^2\text{—}CH_2\text{=}CHR)Pd^0(PPh_3)_2(OAc)^-$ (R = Ph, CO_2Me), the concentration of $Pd^0(PPh_3)_2(OAc)^-$ decreases, making the oxidative addition slower (Scheme 1.16) [34].



Scheme 1.16

1.3.2.2 Oxidative Addition of Aryl Triflates

Mosleh and Jutand have established that the oxidative addition of aryl triflates ($ArOSO_2CF_3$) to $Pd^0(PPh_3)_4$ gives in DMF the cationic complex *trans*-$ArPd(DMF)L_2^+$ as characterized by conductivity measurements (Scheme 1.17a) [35, 36]. When the same reaction is performed from $Pd^0(PPh_3)_2(OAc)^-$ generated from $Pd(OAc)_2$ and 3 equiv PPh_3, the neutral complex *trans*-$ArPd(OAc)L_2$ is formed in equilibrium with the cationic complex (Scheme 1.17b) [37]. This again emphasizes the important role of acetate ions delivered by the precursor $Pd(OAc)_2$.



Scheme 1.17

1.3.3 Complexation/Insertion of the Alkene

In the mechanism postulated by Heck (Scheme 1.8), *trans*-$PhPdIL_2$ was proposed to be formed in the oxidative addition and to react with the alkene. However, such a complex is not generated in the oxidative addition when the precursor is $Pd(OAc)_2$ (Scheme 1.15). Moreover, one sees in Table 1.1, which presents the comparative reactivity of *trans*-$PhPdX(PPh_3)_2$ (X = I, OAc, BF_4) with styrene, that *trans*-$PhPdI(PPh_3)_2$ is inert towards styrene (100 equiv) in DMF at 20 °C. It is only after addition of AcO^- ions that (*E*)-stilbene is formed [29]. Indeed, acetate ions react with *trans*-$PhPdI(PPh_3)_2$ to generate *trans*-$PhPd(OAc)(PPh_3)_2$ (Scheme 1.18 [18, 29]) which reacts with styrene. *trans*-$PhPd(OAc)(PPh_3)_2$ generated in the oxidative addition of PhI to $Pd^0(PPh_3)_2(OAc)^-$ reacts with styrene to give (*E*)-stilbene (Table 1.1). The reaction is retarded by excess PPh_3 [29].

$$PhPdIL_2 + AcO^- \underset{}{\overset{K}{\rightleftharpoons}} PhPd(OAc)L_2 + I^- \quad (L = PPh_3,\ K = 0.3\ (DMF);\ 1.3\ (THF)\ at\ 25\ ^\circ C)$$

Scheme 1.18

This is rationalized by the mechanisms depicted in Scheme 1.19 [1m]. The reaction of the alkene with *trans*-$PhPdI(PPh_3)_2$ is limited by the dissociation of PPh_3 (Scheme 1.19a), whereas the dissociation of one PPh_3 in *trans*-$PhPd(OAc)(PPh_3)_2$ is assisted by the bidentate character of the acetate ligand (Scheme 1.19b). This favours the approach of the alkene in a *cis* position relative to the Ph group.

The following reactivity order is observed in DMF at 20 °C (Table 1.1):

$$trans\text{–}PhPd(OAc)(PPh_3)_2 > trans\text{–}PhPd(DMF)(PPh_3)_2^+ \gg trans\text{–}PhPdI(PPh_3)_2$$

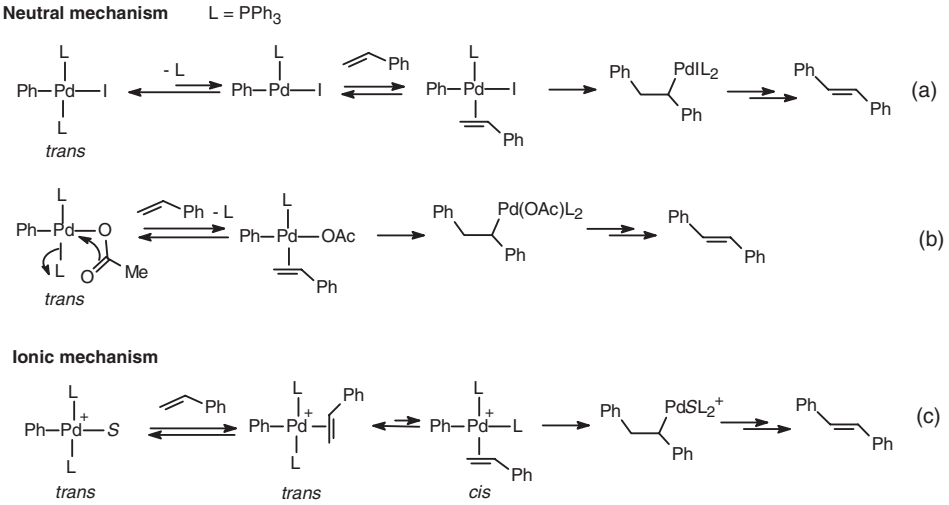
As expected, the cationic complex *trans*-$PhPd(DMF)(PPh_3)_2^+$ is more reactive towards styrene than *trans*-$PhPdI(PPh_3)_2$ but, surprisingly, is less reactive than $PhPd(OAc)(PPh_3)_2$ (Table 1.1) [29, 38]. The coordination of the cationic complex by the alkene gives a *trans* complex (Scheme 1.19c). Consequently, the insertion of the alkene is inhibited by the endergonic *trans*/*cis* isomerization of the alkene-ligated cationic complex, making route c slower than route b.

The amine NEt_3, which may be used as a base in Mizoroki–Heck reactions, does not play any role when the reaction of styrene is performed with isolated *trans*-$PhPdIL_2$ or *trans*-$PhPdSL_2^+$ (Table 1.1). The reaction is, however, accelerated by the amine when performed with *trans*-$PhPd(OAc)L_2$ generated in the oxidative addition of PhI to $Pd^0(PPh_3)_2(OAc)^-$ (formed *in situ* from $Pd(OAc)_2$ and 3 PPh_3) (Table 1.1). Protons are generated together with the Pd(0) complex (Scheme 1.13). Their interaction with the acetate ions shifts the equilibrium between $PhPd(OAc)L_2$ and $PhPdSL_2^+$ towards the latter, which is the less reactive one (Scheme 1.20). Addition of a base neutralizes the protons, increases the concentration of free acetate and, thus, that of the most reactive complex $PhPd(OAc)L_2$, making the overall carbopalladation step faster (Scheme 1.20) [1m]. Consequently, *trans*-$PhPd(OAc)(PPh_3)_2$ is a key intermediate in the carbopalladation step in Mizoroki–Heck reactions when the catalytic precursor is $Pd(OAc)_2$ associated with PPh_3.

Table 1.1 *Reaction of* trans-*$PhPdX(PPh_3)_2$ (X = I, OAc, BF_4) (2 mM) with styrene (0.2 M) in the presence or not of NEt_3 in DMF at 20 °C*

trans-$PhPdX(PPh_3)_2$	NEt_3 (equiv)	Time (h)	(*E*)-stilbene yield (%)
$PhPd(OAc)L_2$[a]	0	24	34
$PhPd(OAc)L_2$[a]	3	19	75
$PhPdIL_2$	0 or 3	24	0
$PhPdIL_2 + 2\ AcO^-$	0 or 3	48	72
$PhPdSL_2^+, BF_4^-$	0 or 3	24	27

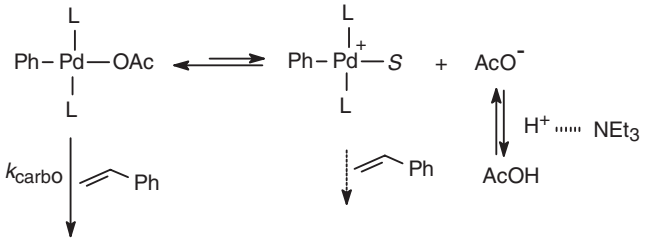
[a] *trans*-$PhPd(OAc)(PPh_3)_2$ is generated by oxidative addition of PhI (2 mM) to $Pd(PPh_3)_2(OAc)^-$ generated from $Pd(OAc)_2$ (2 mM) and 3 equiv PPh_3 in DMF.



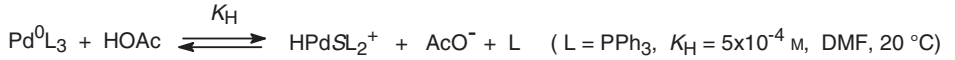
Scheme 1.19

1.3.4 Multiple Role of the Base

In summary, the base serves multiple purposes in Mizoroki–Heck reactions: (i) the base stabilizes $Pd^0(PPh_3)_2(OAc)^-$ versus its decomposition to $Pd^0(PPh_3)_2$ by protons (Scheme 1.14); (ii) the base slows down the oxidative addition; (iii) the base accelerates the carbopalladation step by increasing the concentration of the reactive $PhPd(OAc)L_2$ (Scheme 1.20); (iv) the base favours the recycling of the Pd(0) complex from the hydridopalladium(II) (formed in the β-hydride elimination process) by shifting the reversible reductive elimination towards the Pd(0) complex. The formation of $HPdXL_2$ (X = I, L = PPh_3) has been proposed by Heck (Scheme 1.8). In the present case, where acetate ions play such an important role, it is not clear whether $HPdI(PPh_3)_2$ exists or not. In DMF, the cationic complex *trans*-$HPdSL_2^+$ may be formed with acetate (or iodide) as the counter anion. It has indeed been shown that the oxidative addition of Pd^0L_4 (L = PPh_3) with acetic acid is reversible (Scheme 1.21) and that the hydridopalladium complex formed in that reaction is cationic, $HPd(DMF)(PPh_3)_2^+$ [36, 39]. One sees that the role of the base is more subtle than initially postulated. The consequences in terms of efficiency of the catalytic cycle are now presented.



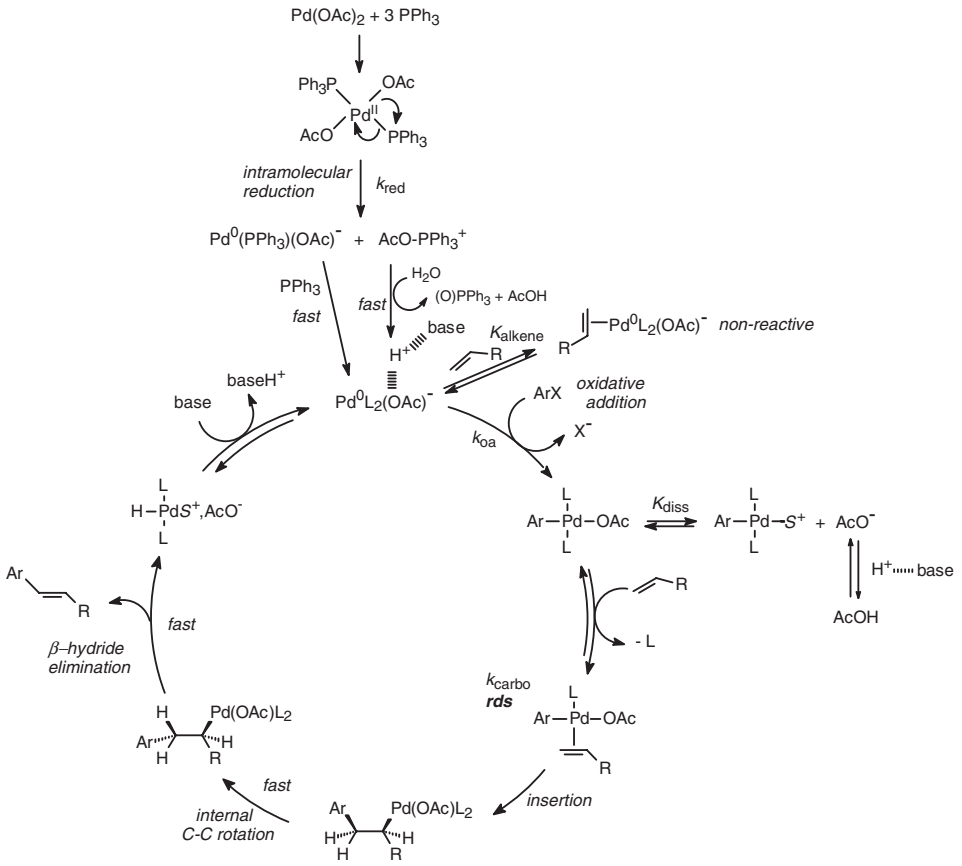
Scheme 1.20



Scheme 1.21

1.3.5 Catalytic Cycle

A mechanism is now proposed for Mizoroki–Heck reactions involving $Pd(OAc)_2$ as precursor associated with PPh_3 (Scheme 1.22). From the rate constants of the main steps given in Scheme 1.22, it appears that, for comparable iodobenzene and styrene concentrations, the overall carbopalladation (complexation/insertion of the alkene) from $PhPd(OAc)(PPh_3)_2$



Scheme 1.22 *Mechanism of Mizoroki–Heck reactions with $Pd(OAc)_2$ as precursor associated with PPh_3. Rate and equilibrium constants in DMF at 25 °C when ArX = PhI, R = Ph and base = NEt_3: $k_{red} = 4 \times 10^{-4}\ s^{-1}$, $K_{alkene} = 61\ M^{-1}$, $k_{oa} = 140\ M^{-1}\ s^{-1}$ ($65\ M^{-1}\ s^{-1}$ in the presence of 3 equiv NEt_3), $K_{diss} = 1.4 \times 10^{-3}$ M, $k_{carbo} = 5 \times 10^{-5}\ M^{-1}\ s^{-1}$ ($10^{-4}\ M^{-1}\ s^{-1}$ in the presence of 3 equiv NEt_3), k_{carbo} is the apparent rate constant of the overall carbopalladation process, which involves complexation and insertion of the alkene.*

is the slowest step of the catalytic cycle. This new mechanism highlights the crucial role of acetate ions which are delivered by the precursor $Pd(OAc)_2$. Indeed, AcO^- is a ligand of all the Pd(0) and Pd(II) complexes present throughout the catalytic cycle, principally in $PhPd(OAc)L_2$ involved in the rate-determining step.

1.3.5.1 Factors Controlling the Efficiency of a Catalytic Reaction

When the successive steps of a catalytic cycle are examined independently from each other, they have their own reaction rate. But when they are involved in a catalytic cycle, the effective rates of the successive steps are not independent from each other. Indeed, the rate of step i is $v_i = k_i[R_i][M_i]$, where k_i is the rate constant of step i, R_i is the reagent involved in step i and M_i is the catalytic species involved in step i, whose concentration $[M_i]$ is modulated, controlled by the rate of the previous reaction $(i - 1)$ in which it is generated [1k]. All steps have the same reaction rate when the stationary regime is reached. It will be more easily reached if the intrinsic reaction rates of all elemental steps are as close as possible to each other. In other words, to increase the efficiency of a catalytic cycle one must accelerate the rate-determining step; that is, destabilize the stable intermediate species and also decelerate the fast reactions by stabilizing high-energy species [1k].

This is illustrated in the mechanism of the Mizoroki–Heck reaction depicted in Scheme 1.22. Indeed, three main factors contribute to slow down the fast oxidative addition of PhI: (i) *the anion* AcO^- delivered by the precursor $Pd(OAc)_2$, which stabilizes Pd^0L_2 as the less reactive $Pd^0L_2(OAc)^-$; (ii) *the base* (NEt_3) which indirectly stabilizes $Pd^0L_2(OAc)^-$ by preventing its decomposition by protons to the more reactive bent Pd^0L_2; (iii) *the alkene* by complexation of $Pd^0L_2(OAc)^-$ to form the nonreactive $(\eta^2\text{-}CH_2{=}CHR)Pd^0L_2(OAc)^-$. On the other hand, the slow carbopalladation is accelerated by the *base* and by the *acetate ions* which generate $ArPd(OAc)L_2$, which in turn is more reactive than the postulated $ArPdIL_2$. The base, the alkene and the acetate ions play, then, the same dual role in Mizoroki–Heck reactions: deceleration of the oxidative addition and acceleration of the slow carbopalladation step. Whenever the oxidative addition is fast (e.g. with aryl iodides or activated aryl bromides), this dual effect favours the efficiency of the catalytic reaction by bringing the rate of the oxidative addition closer to the rate of the carbopalladation [1m, 34].

The mechanism depicted in Scheme 1.22 is also valid for Mizoroki–Heck reactions performed with aryl triflates, since $ArPd(OAc)L_2$ complexes are formed in the oxidative addition (Scheme 1.17b) [37]. This mechanism is also applicable when the catalytic precursor is not $Pd(OAc)_2$ (e.g. $Pd^0(dba)_2$ and PPh_3, $PdCl_2(PPh_3)_2$ or $Pd^0(PPh_3)_4$ (dba = *trans*,*trans*-dibenzylideneacetone)), but when acetate ions are used as base. AcO^- is indeed capable of coordinating to Pd^0L_2 complexes to give $Pd^0L_2(OAc)^-$ [29] or react with $ArPdIL_2$ to generate the more reactive $ArPd(OAc)L_2$ [18].

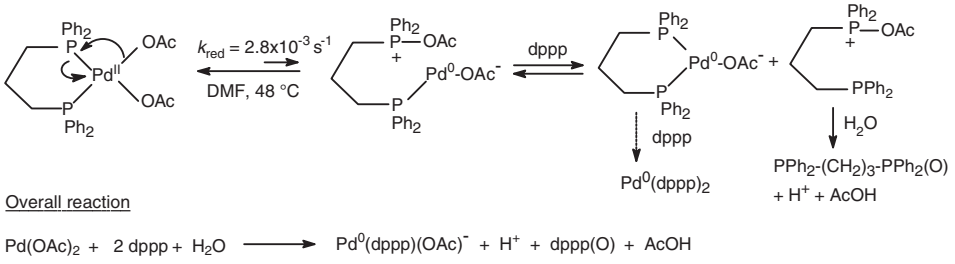
The situation is problematic when considering less reactive aryl chlorides or deactivated aryl bromides involved in the rate-determining oxidative addition, since the alkene will also contribute to decelerate the slow oxidative addition by complexation of the reactive $Pd^0L_2(OAc)^-$ (Scheme 1.16). To solve this problem, one has to design a new ligand which will make the Pd(0) more reactive or introduce the alkene via a syringe pump, so that a low alkene concentration can be maintained throughout the catalytic reaction.

1.4 Mechanism of the Mizoroki–Heck Reaction when the Catalytic Precursor is $Pd(OAc)_2$ Associated with Bisphosphine Ligands

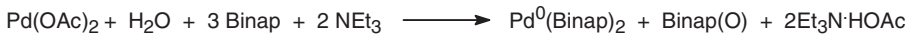
In 1990, Cabri *et al*. [40a] reported that the precursor $Pd(OAc)_2$ associated with a bidentate P^P ligand as dppp (1,3-bis-diphenylphosphinopropane) appeared to be more efficient than PPh_3 in Mizoroki–Heck reactions performed from aryl triflates and enol ethers (electron-rich alkenes); moreover, the regioselectivity in favour of the α-arylated alkenes was improved to 100%. Since that time, dppp associated with $Pd(OAc)_2$ has been used extensively to catalyse Mizoroki–Heck reactions and to investigate the factors that control the regioselectivity [1g, 40]. The chiral bidentate (*R*)-Binap (2,2′-bis(diphenylphosphino)-1,1-binaphthyl) associated with $Pd(OAc)_2$ has also been used by Shibasaki and coworkers [2b,d, 41a] and Overman and Poon [41b] in intramolecular enantioselective Mizoroki–Heck reactions (also, see Link [2f] for an authorative review on the Overman–Shibasaki chemistry), as well as by Hayashi and coworkers [2a, 41c,d] to control the regioselectivity and enantioselectivity of intermolecular Mizoroki–Heck reactions performed from cyclic alkenes (see Schemes 1.3 and 1.2 (Z = O) respectively).

1.4.1 Pd(0) Formation from Precursor

As established by Amatore, Jutand *et al*. in 2001 [42], the reaction of $Pd(OAc)_2$ associated with 1 equiv of dppp does not generate an observable Pd(0) complex. This is a consequence of the reversibility of the reductive elimination which takes place within $Pd(OAc)_2$(dppp) formed in the early stage (Scheme 1.23). The intramolecular and, consequently, fast reverse reaction is an oxidative addition of the resulting Pd(0) complex to the phosphonium formed in the reductive elimination step but still ligated to the Pd(0) (Scheme 1.23). As a consequence, a Pd(0) complex is generated at low concentration in that endergonic equilibrium. However, if a second equivalent of dppp is added, then the anionic Pd(0) complex $Pd^0(dppp)(OAc)^-$ is formed by substitution of the mono-ligated $P^{\wedge}P^+$ (Scheme 1.23). The hydrolysis of the latter, which gives protons and the hemioxide dppp(O), contributes to the shift of the successive equilibria towards the formation of the anionic Pd(0) complex. The formation of the stable anionic $Pd^0(dppp)(OAc)^-$ complex is supported by DFT calculations [30]. As for $Pd^0(PPh_3)_2(OAc)^-$, $Pd^0(dppp)(OAc)^-$ is more stable in the presence of a base such as NEt_3. Indeed, $Pd^0(dppp)(OAc)^-$ may be decomposed into the unstable naked Pd^0(dppp) by interaction of its ligand acetate with protons formed together with



Scheme 1.23



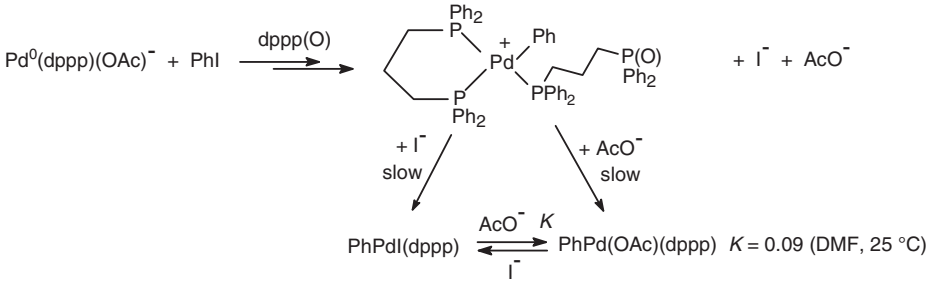
Scheme 1.24

the Pd(0) complex (process similar to that in Scheme 1.14 for PPh_3). Neutralization of the protons by NEt_3 stabilizes the anionic $Pd^0(dppp)(OAc)^-$ [42]. Addition of a third equivalent of dppp generates $Pd^0(dppp)_2$. The rate of formation of the Pd(0) complex from $Pd(OAc)_2$ and 2 equiv dppp (see k_{red} in Scheme 1.23) is slightly slower than that from $Pd(OAc)_2$ and 3 equiv PPh_3 in DMF at the same temperature [20, 42].

The formation of $Pd^0((R)\text{-Binap})_2$ and (*R*)-Binap(O) from $Pd(OAc)_2$ and 3 equiv of (*R*)-Binap in benzene was reported earlier by Ozawa *et al*. in 1992 [19]. Owing to excess (*R*)-Binap, the overall reaction gives $Pd^0((R)\text{-Binap})_2$ (Scheme 1.24). The reaction is performed in the presence of NEt_3. Water is found to be a crucial additive, with the formation of the Pd(0) complex being faster in the presence of water [19]. The mechanism of formation of $Pd^0(Binap)_2$ must be similar to that involving dppp (Scheme 1.23). The intramolecular reduction process is reversible and the role of water is to shift the successive equilibria (similar to those in Scheme 1.23 with (*R*)-Binap instead of dppp) towards the formation of the final $Pd^0(Binap)_2$ by the irreversible hydrolysis of the phosphonium salt. ^{18}O-labelled (*R*)-Binap(O) is indeed formed over time when using $^{18}OH_2$ [19]. Interestingly, the accelerating effect of water in the reduction process is specific to bidentate ligands. It is not observed with PPh_3 (Scheme 1.13) [18] because the intramolecular reduction process which delivers the Pd(0) complex is in that case rendered irreversible because of a much slower backward oxidative addition (intermolecular reaction).

1.4.2 Oxidative Addition

Owing to the presence of the hemioxide dppp(O) formed together with $Pd^0(dppp)(OAc)^-$, the oxidative addition of PhI does not form the expected PhPdI(dppp) complex; rather, the cationic complex $PhPd(dppp)(dppp(O))^+$, ligated by both the dppp ligand and the hemioxide which behaves as a monodentate ligand (Scheme 1.25) [42], is formed. The mechanism of the oxidative addition is quite complicated, involving dimeric anionic Pd(0) complex, and the overall reaction is slower (by a factor 300) than that performed from $Pd^0(PPh_3)_2(OAc)^-$ at identical concentrations of PhI and NEt_3 [42]. The complex $PhPd(dppp)(dppp(O))^+$ reacts with excess iodide or acetate ions to give PhPdI(dppp) and PhPd(OAc)(dppp)

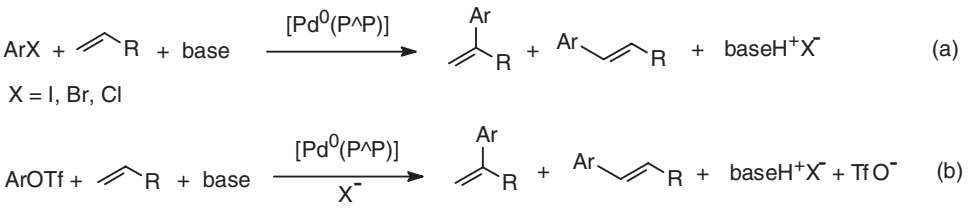


Scheme 1.25

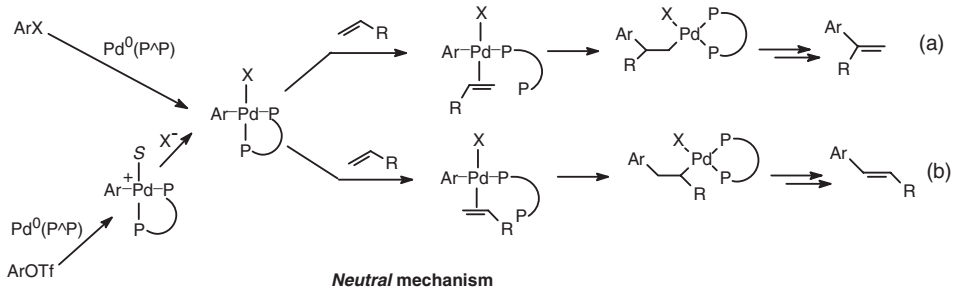
respectively [42]. Moreover, those two complexes are able to exchange their anions in a reversible reaction (Scheme 1.25) [43].

1.4.3 Complexation/Insertion of the Alkene–Regioselectivity

Regioselectivity is one of the major problems of Mizoroki–Heck reactions. It is supposed to be affected by the type of mechanism: *ionic* versus *neutral*, when the palladium is ligated by bidentate P^P ligands. The ligand dppp has been taken as a model for the investigation of the regioselectivity. Cabri and Candiani [1g] have reported that a mixture of branched and linear products is formed in Pd^0(P^P)-catalysed Mizoroki–Heck reactions performed from electron-rich alkenes and aryl halides (Scheme 1.26a) or aryl triflates in the presence of halide ions (Scheme 1.26b). This was rationalized by the so-called *neutral* mechanism (Scheme 1.27). The neutral complex ArPdX(P^P) is formed in the oxidative addition of Pd^0(P^P) to aryl halides or to aryl triflates in the presence of halides. The carbopalladation proceeds from the neutral ArPdX(P^P) after dissociation of one phosphorus. The coordination of the alkene may proceed in two ways, leading to a mixture of linear and branched alkenes (Scheme 1.27). This mechanism involving *neutral* complexes is more sensitive to steric factors than to electronic factors with a preferential migration of the aryl group onto the less substituted carbon of the alkene, leading to the linear alkene (Scheme 1.27b). This mechanism was also proposed by Cabri and Candiani [1g] for electron-deficient alkenes which are even more reactive towards neutral complexes than electron-rich alkenes. Cabri and Candiani [1g] and Hayashi *et al*. [2a] have reported that branched alkenes are mainly produced from electron-rich alkenes in Pd^0(P^P)-catalysed Mizoroki–Heck reactions



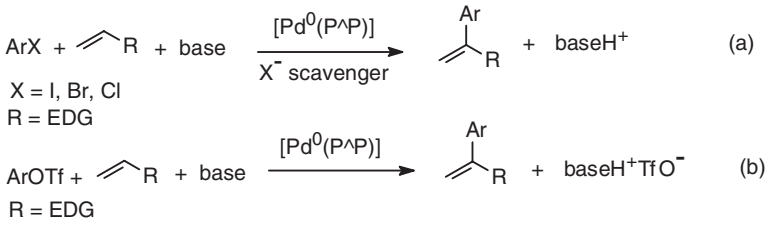
Scheme 1.26



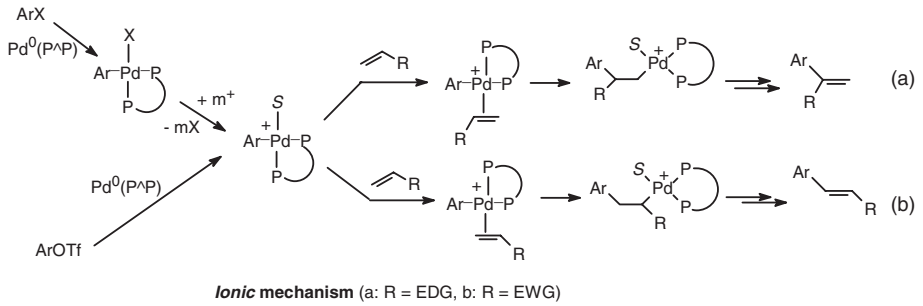
Scheme 1.27 *Textbook* neutral *mechanism for the regioselectivity of Mizoroki–Heck reactions (the C—C internal rotation is not shown).*

performed from aryl halides in the presence of a halide scavenger (Ag^+ [40c,d, 44a,b], Tl^+ [40c,d, 44c], K^+ in aqueous DMF [40j]) (Scheme 1.28a) or from aryl triflates (Scheme 1.28b) [40a,d,e,g, 41c,d]. Since cationic complexes ArPd*S*(P^P)$^+$ (*S* = solvent) may be generated by (i) dissociation of ArPdX(P^P) [45], (ii) abstraction of X in ArPdX(P^P) by a halide scavenger [46, 47] or (iii) by oxidative addition of aryl triflates to Pd^0(P^P) complexes [48], they have been proposed in the reaction with alkenes in the so-called *ionic* mechanism; that is, involving *cationic* Pd(II) complexes (Scheme 1.29). The carbopalladation proceeds by coordination of the alkene to the cationic ArPd*S*(P^P)$^+$. This *ionic* mechanism is more sensitive to electronic factors than to steric factors. When R = EDG, the coordination of the polarized alkene proceeds in one major pathway with a selective migration of the aryl moiety onto the charge-deficient α-carbon of the electron-rich alkene, leading to the branched alkene (α-arylation) (Scheme 1.29a) [1g, 49].

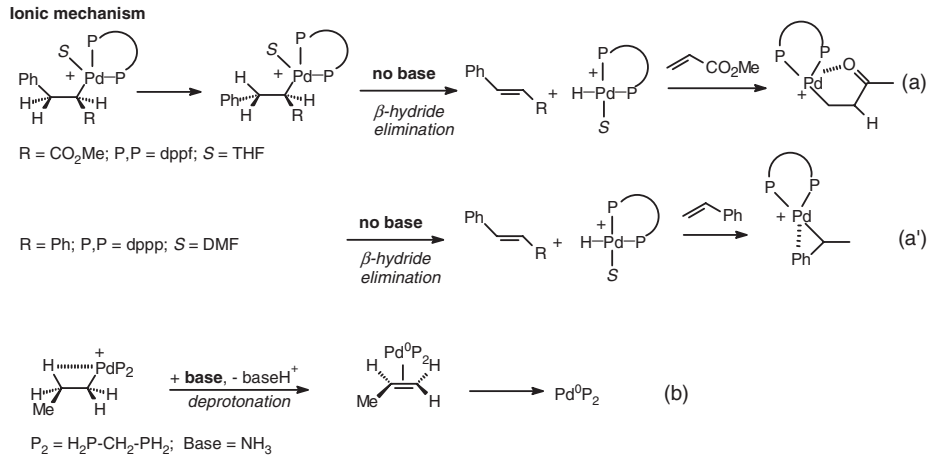
The *ionic* mechanism has been investigated from isolated cationic complexes ArPd*S*(P^P)$^+$ at low temperatures so that the σ-alkyl–Pd*S*(P^P)$^+$ intermediates can be observed after reaction with alkenes CH_2=CHR. In the absence of a base, Brown and Hii [46] have characterized σ-ArCH_2CH(R)–Pd(THF)(dppf)$^+$ (Ar = Ph, R = CO_2Me; dppf = 1,1′-bis(diphenylphosphino)ferrocene) by ^{1}H and ^{31}P NMR spectroscopy. The β-hydride elimination takes place, leading to the linear alkene (*E*)-ArCH=CHR and HPd(THF)(dppf)$^+$. The latter cannot generate a Pd^0 complex in the absence of a base and reacts with the initial alkene (Scheme 1.30a). Similarly, when reacting PhPd(THF)(Binap)$^+$ with the electron-rich alkene 2,3-dihydrofuran, the intermediate σ-alkyl–Pd(THF)(Binap)$^+$ is observed and HPd(THF)(Binap)$^+$ is also found to react with the initial 2,3-dihydrofuran [50]. At −60 °C, σ-ArCH_2CH(Ar′)–Pd(THF)(dppp)$^+$ complexes are stabilized by interaction of the Pd^{II} centre with the adjacent Ar′ group, which restricts the C—C internal rotation [51].



Scheme 1.28



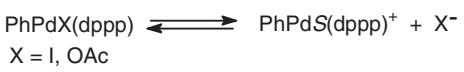
Scheme 1.29 *Textbook* ionic *mechanism for the regioselectivity of Mizoroki–Heck reactions.*



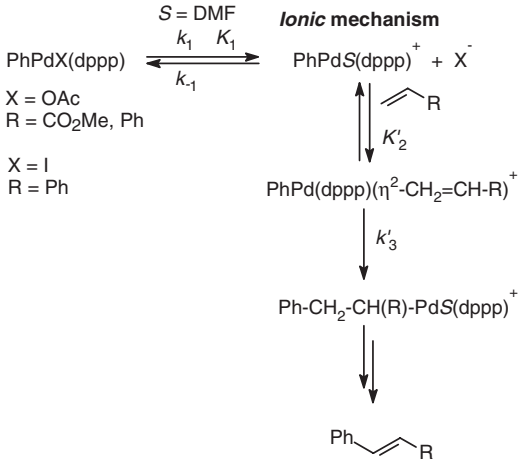
Scheme 1.30 Ionic *mechanism: (a) Experimental work. (a′) Experimental work. The branched alkene* $Ph_2C{=}CH_2$ *is also formed. (b) DFT calculations.*

Åkermark and coworkers [47] have characterized σ-$PhCH_2CH(R)$–Pd(DMF)(dppp)$^+$ (R = Ph) formed by reacting PhPd(dppp)$^+BF_4^-$ with styrene in DMF at $-20\,^\circ$C. This complex delivers (*E*)-stilbene and HPd(DMF)(dppp)$^+$ which reacts with styrene in the absence of a base (Scheme 1.30a′). Therefore, in the absence of a base the hydridopalladium is quenched by the starting alkene and no Pd(0) is formed. Supported by DFT calculations, Deeth *et al*. [52] have proposed that a Pd^0 complex is generated directly from the cationic σ-alkyl–Pd(II) adduct in the presence of a base, via the easier deprotonation of the agostic hydrogen (Scheme 1.30b); the energetically less favoured β-hydride elimination is therefore bypassed.

Amatore, Jutand *et al*. [42] have established that the oxidative addition of PhI to Pd^0(OAc)(dppp)$^-$ (generated from $Pd(OAc)_2$ and 2 equiv dppp) gives the cationic complex PhPd(dppp)(dppp(O))$^+$; this is followed by reaction of iodide ions released from PhI in the course of a catalytic reaction giving PhPdI(dppp) or/and PhPd(OAc)(dppp) whenever acetate ions are used as bases (Scheme 1.25). The reaction of PhPd(dppp)(dppp(O))$^+$ with alkenes (styrene, methyl acrylate) is so slow that this complex must be considered as a transient complex on the way to PhPdI(dppp) and/or PhPd(OAc)(dppp). These two complexes, which exchange their anions (Scheme 1.25), are in equilibrium with the common cationic complex PhPd(DMF)(dppp)$^+$ in DMF (Scheme 1.31) [43]. Consequently, two *neutral* phenyl–palladium(II) complexes are candidates, in addition to the *cationic* PhPd*S*(dppp)$^+$, for the reaction with alkenes. The kinetics of the reaction of isolated PhPdX(dppp) (X = I, OAc) with electron-deficient, neutral and electron-rich alkenes in the absence of a base has been followed by ^{31}P NMR spectroscopy in DMF. It emerges that PhPd(OAc)(dppp) reacts with styrene and methyl acrylate via PhPd(DMF)(dppp)$^+$; that

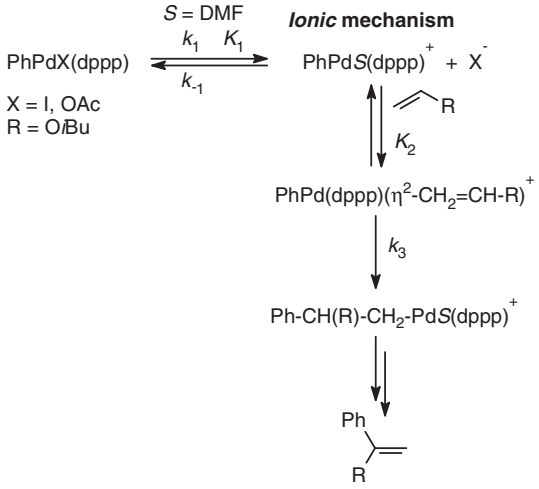


Scheme 1.31

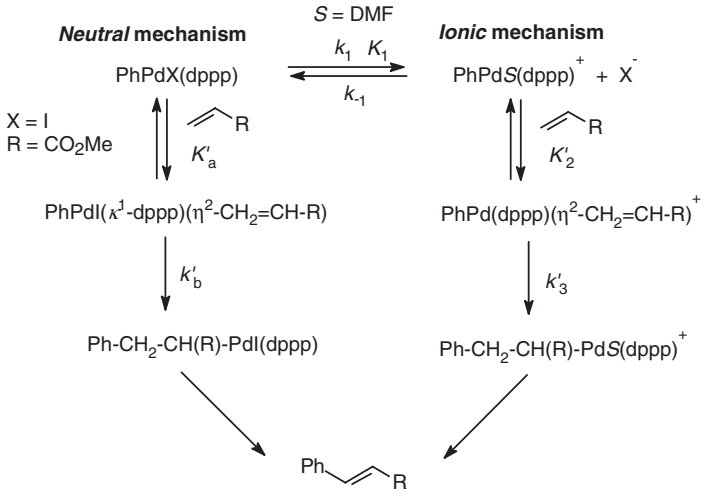


Scheme 1.32 *The reactive species with neutral and electron-deficient alkenes from kinetic data.*

is, via an *ionic* mechanism (Scheme 1.32) [43], as with isobutylvinyl ether (Scheme 1.33) [53]. The mechanism of the reaction of PhPdI(dppp) with alkenes is substrate dependent. PhPdI(dppp) reacts with styrene via PhPd(DMF)(dppp)$^+$ in the *ionic* mechanism (Scheme 1.32) [43], as with isobutylvinyl ether (Scheme 1.33) [53], whereas PhPdI(dppp) and PhPd(DMF)(dppp)$^+$ react in parallel with the more reactive methyl acrylate (*neutral* and *ionic* mechanisms) (Scheme 1.34) [43]. All reactions are retarded by coordinating anions (I^- and AcO^-) at constant ionic strength, which is in agreement with the pure *ionic* mechanisms of Schemes 1.32 and 1.33 and the mixed mechanism of Scheme 1.34, with PhPd(DMF)(dppp)$^+$ being more reactive than PhPdI(dppp). All reactions are accelerated upon increasing the ionic strength. The higher the ionic strength, the higher the concentration of PhPd(DMF)(dppp)$^+$ is and the faster the overall reaction with the alkene. In all



Scheme 1.33 *The reactive species with an electron-rich alkene from kinetic data.*



Scheme 1.34 *The reactive species with an electron-deficient alkene from kinetic data.*

cases, the linear product (*E*)-PhCH=CHR is formed as: (i) the unique product for R = CO_2Me from PhPdX(dppp) (X = I, OAc) [43]; (ii) the major product for R = Ph from PhPdI(dppp) (80% selectivity) and PhPd(OAc)(dppp) (82% selectivity) [47]. The branched product CH=CH(Ph)R is formed as the major product for R = O*i*Bu from PhPdI(dppp) (90% selectivity) [53]. In a first approach, the slower formation of the minor product has not been considered and the alkene insertion step has been regarded as irreversible, as postulated in textbook mechanisms (Schemes 1.27 and 1.29). The equilibrium and rate constants for the formation of the major product have been determined in DMF (Table 1.2) with the following reactivity orders [43, 53]:

- whatever the complex PhPdX(dppp) (X = I, OAc)

$$CH_2{=}CH{-}CO_2Me > CH_2{=}CH{-}O\text{-}i\text{-}Bu > CH_2{=}CH{-}Ph$$

- whatever the alkene

$$PhPd(DMF)(dppp)^+ \gg PhPdX(dppp) \quad (X = I,\ OAc)$$

Table 1.2 *Equilibrium and rate constants of the reaction of PhPdX(dppp) (X = I, OAc) with alkenes in DMF at 25 °C (Schemes 1.32–1.34) [43, 53]*

PhPdX(dppp)		CO_2Me	CO_2Me	O*i*Bu	Ph
X	k_1 (10^{-4} s^{-1})	$k'_a k'_b/(k'_{-a} + k'_b)$ (10^{-5} M^{-1} s^{-1})	$K'_1 K'_2 k'_3$ (10^{-6} s^{-1})	$K_1 K_2 k_3$ (10^{-7} s^{-1})	$K'_1 K'_2 k'_3$ (10^{-8} s^{-1})
OAc	1.6(±0.1)	—	1.5(±0.1)	1.2(±0.1)	6.6(±0.1)
I	1.1(±0.1)	2.5	1.0(±0.1)	1.7(±0.1)	3.8(±0.1)

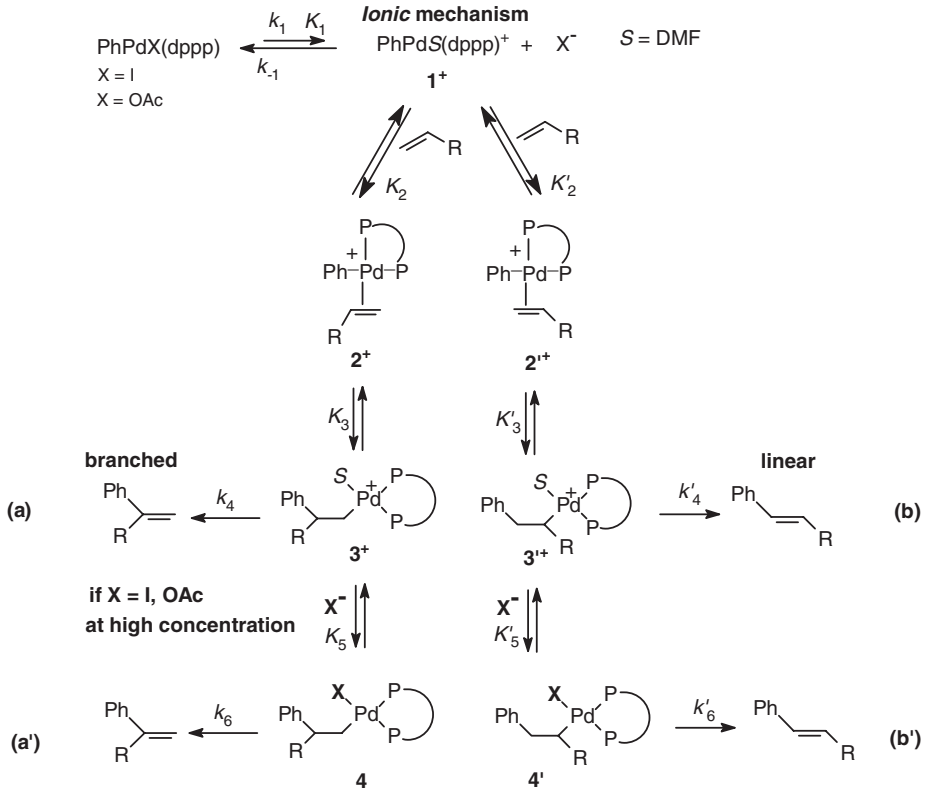
PhPd(OAc)(dppp) is more reactive than PhPdI(dppp) with styrene and methyl acrylate, in agreement with the fact that the dissociation of PhPd(OAc)(dppp) to the reactive PhPd(DMF)(dppp)$^+$ is more effective than that of PhPdI(dppp) (compare the respective values of k_1 in Table 1.2). Interestingly, an inversion of reactivity is observed with the electron-rich isobutylvinyl ether (Table 1.2).

Therefore, except for the reaction of methyl acrylate with PhPdI(dppp), all reactions exclusively proceed from the *cationic* complex PhPd(DMF)(dppp)$^+$. However, the simplified mechanisms established in Schemes 1.32 and 1.33 cannot explain the high dependence of the regioselectivity on experimental conditions. Indeed, Åkermark and coworkers [47] have reported reactions of isolated PhPdX(dppp) (X = I, OAc, BF_4) with styrene, focusing on the effect of X on the regioselectivity of the reaction. In DMF, the ratio PhCH=CHPh/CH_2=CPh_2 decreases in the order OAc > I > BF_4. According to the mechanism proposed in Scheme 1.32, which establishes the exclusive reactivity of styrene with the *cationic* complex PhPd(DMF)(dppp)$^+$ generated from PhPdX(dppp) (X = I, AcO), all complexes PhPdX(dppp) (X = I, AcO, BF_4) should afford the same regioselectivity, namely that given by the cationic complex PhPd(DMF)(dppp)$^+BF_4{}^-$, which is not observed experimentally [47].

In more recent studies by Xiao and coworkers [40m,n], Mizoroki–Heck reactions catalysed by $Pd(OAc)_2$ associated with dppp and performed from the electron-rich alkene (*n*-butylvinyl ether) and aryl halides (without any halide scavenger, i.e. under the conditions of the textbook *neutral* mechanism of Scheme 1.27 proposed by Cabri and Candiani [1g]) give a mixture of branched and linear products in DMF, whereas the branched product is exclusively produced in ionic liquids (in the absence of halide scavengers) in a faster reaction. Whatever the medium, the *cationic* complex ArPd*S*(dppp)$^+$ is always the sole reactive complex with electron-rich alkene (Scheme 1.33) [53]. Consequently, the regioselectivity should not vary with the experimental conditions.

A more elaborated mechanism was thus proposed by Jutand and coworkers [53] which rationalizes the regioselectivity of Mizoroki–Heck reactions performed in DMF with dppp as ligand (Scheme 1.35). The complexation of the alkene to the reactive cationic complex PhPd(DMF)(dppp)$^+$ (**1**$^+$) may generate the two isomers **2**$^+$ and **2**′$^+$ and then complexes **3**$^+$ and **3**′$^+$ in a reversible insertion step [54]. When considering electron-rich alkenes, the branched product is formed as a major product because $K_2K_3k_4 \gg K'_2K'_3k'_4$ (Scheme 1.35, route a). If anion X^- (I^-, AcO^-) is present at high concentration, cationic complexes **3**$^+$ and **3**′$^+$ may be reversibly quenched by the anion as neutral complexes **4** and **4**′ respectively. The linear product will be formed as a major product whenever $K'_2K'_3K'_5k'_6[X^-] \gg K_2K_3k_4$ (route b′ faster than route a in Scheme 1.35) or $K'_2K'_3K'_5k'_6 \gg K_2K_3K_5k_6$ if $K_5k_6[X^-] \gg k_4$ (route b′ faster than route a′).

According to Scheme 1.35, the major branched product will be formed from an electron-rich alkene in a reaction involving either pure *cationic* PhPd(DMF)(dppp)$^+$ or *neutral* PhPdX(dppp) which reacts via the *cationic* complex, both in the absence of extra anions (I^-, AcO^-) (Scheme 1.35, route a). The linear product will be formed if the reaction is performed in the presence of a large excess of anions (I^-, AcO^-), as it often occurs in real catalytic reactions, but still via the *cationic* PhPd(DMF)(dppp)$^+$ (Scheme 1.35, route b′). The inversion of reactivity observed in the reaction of the electron-rich isobutylvinyl ether – PhPdI(dppp) being more reactive than PhPd(OAc)(dppp) (Table 1.2 [53]), although it is less dissociated to the cationic complex – may be understood as the contribution of the



Scheme 1.35 *Mechanism which rationalizes the regioselectivity of Mizoroki–Heck reactions in DMF when P^P = dppp (the C—C internal rotation in complexes* $\mathbf{3}^+$*,* $\mathbf{3'}^+$*,* $\mathbf{4}$ *and* $\mathbf{4'}$ *is omitted for more clarity).*

formation of the branched product via route a′ in parallel to route a (Scheme 1.35). In that case, what would be determined is not $K_1K_2k_3$ (as proposed in Table 1.2 when the alkene insertion was considered as irreversible) but $K_1K_2K_3k_4 + K_1K_2K_3K_5k_6[X^-] = K_1K_2K_3(k_4 + K_5k_6[X^-])$. Since K_2K_3 does not depend on X, one has to compare the values of $K_1(k_4 + K_5k_6[X^-])$ for PhPd(OAc)(dppp) and PhPdI(dppp). One knows that PhPd(OAc)(dppp) is more dissociated than PhPdI(dppp) towards the cationic complex (${K_1}^{OAc} > {K_1}^{I}$), but one does not know the relative values of K_5k_6 for AcO^- or I^-. The affinity of AcO^- for complex $\mathbf{3}^+$ must be lower than that of I^- (${K_5}^{OAc} < {K_5}^{I}$), suggesting an antagonist effect and thus an inversion of the reactivity.

As far as the less polarized styrene is concerned, routes a and b in Scheme 1.35 are in competition in the reaction of the isolated *cationic* $PhPd(DMF)(dppp)^+$ with styrene, leading to a mixture of linear *l* and branched *b* products (*b*/*l* = 42/58 [47]). The reaction of styrene with *neutral* PhPdX(dppp) (X = I, OAc), both reacting via the *cationic* complex, gives the major linear product (*b*/*l* = 20/80 and 18/82 respectively [47]) because the faster reaction of I^- and AcO^- with $\mathbf{3'}^+$ favours route b′ in Scheme 1.35.

In the catalytic reactions of Xiao and coworkers [40m,n] performed in DMF from aryl bromides and *n*-butylvinyl ether, a mixture of branched and linear products is formed

because the halide ions released at high concentration in the course of the catalytic reaction react with the *cationic* complexes of type $\mathbf{3}^+$ and $\mathbf{3}'^+$ to give the *neutral* complexes **4** and **4′**; this accounts for the mixture of branched and linear products. At high ionic strength, such as in ionic liquids, the dissociation of ArPdX(dppp) towards the reactive *cationic* complex ArPd*S*(dppp)$^+$ is favoured, its concentration is increased and, consequently, the reaction must be faster, which is observed. But more importantly, the reaction of halide ions with the cationic complexes of type $\mathbf{3}^+$ and $\mathbf{3}'^+$ is slowed down by the high ionic strength (consequently, no need of halides scavengers), inhibiting the formation of complexes **4** and **4′** (lower part of Scheme 1.35). The regioselectivity of the reaction performed in ionic liquids (major branched product) is thus given by the route a of Scheme 1.35, via the major cationic complexes $\mathbf{2}^+/\mathbf{3}^+$.

1.4.4 Catalytic Cycles

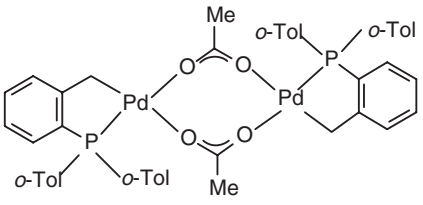
As established above, the regioselectivity of Mizoroki–Heck reactions performed in DMF is sensitive to the presence of coordinating anions such as halide or acetate (Scheme 1.35). The carbopalladation step always proceeds from the more reactive *cationic* complex ArPd*S*(dppp)$^+$ (Schemes 1.35 and 1.36), not from *neutral* ArPdX(dppp), except for the reaction of ArPdI(dppp) with the most reactive methyl acrylate, performed in the absence of acetate ions (Schemes 1.34 and 1.37).

At identical concentrations of iodobenzene and alkenes CH_2=CHR (R = Ph, CO_2Et, O*i*Bu), the oxidative addition is always faster [42] than the reaction of alkene with PhPdX(dppp), which is the rate-determining step (DMF, 25 °C) [43, 53].

1.5 Mechanism of the Mizoroki–Heck Reaction when the Catalytic Precursor is a *P*,*C*-Palladacycle

1.5.1 Pd(0) Formation from a *P*,*C*-Palladacycle

In contrast to PPh_3, P(*o*-Tol)$_3$ cannot reduce $Pd^{II}(OAc)_2$ to a Pd(0) complex, but a *P*,*C*-palladacycle, *trans*-di(μ-acetato)-bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium (**5**) is formed via a cyclometallation [27, 55]. The palladacycle **5** is an efficient catalyst for Mizoroki–Heck reactions involving aryl bromides and activated aryl chlorides (i.e. substituted by EWGs) [1j,l,o,s–v, 27, 55]. When **5** is used as catalyst in C—N cross-coupling reactions, Louie and Hartwig [56] have established that the true catalyst is a Pd(0) complex, $Pd^0\{P(o\text{-Tol})_3\}_2$ formed by reduction of the palladacycle by the nucleophile (a secondary amine as a hydride donor in the presence of a strong base).



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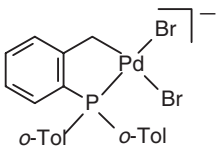

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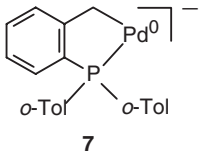

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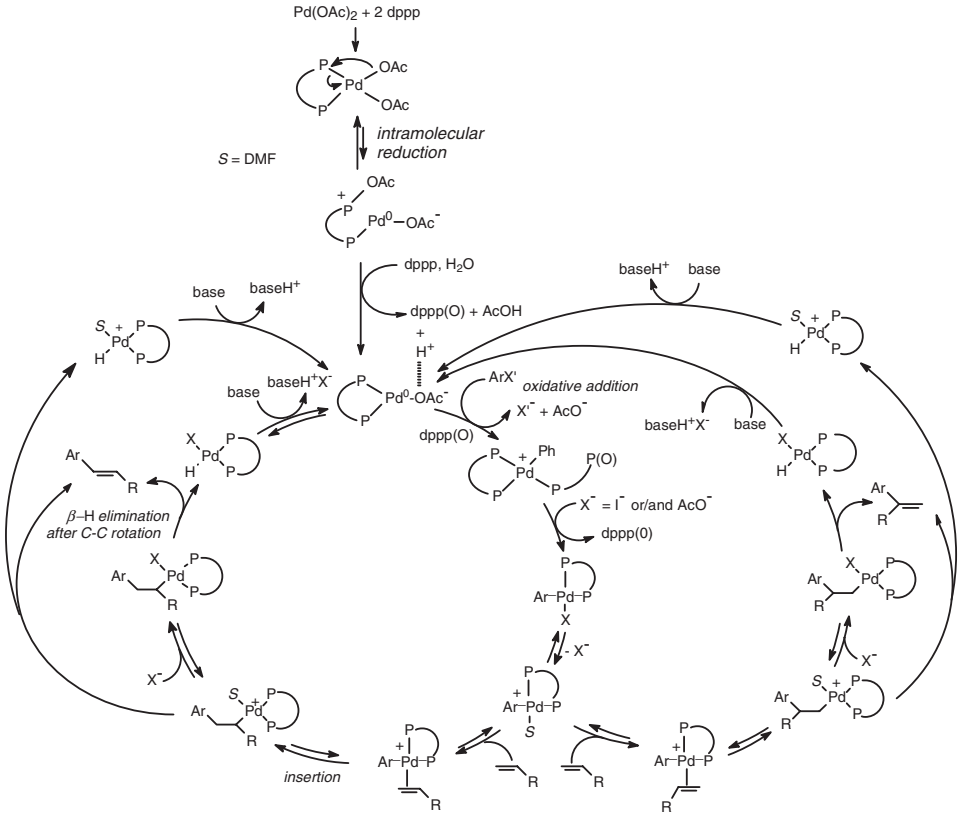
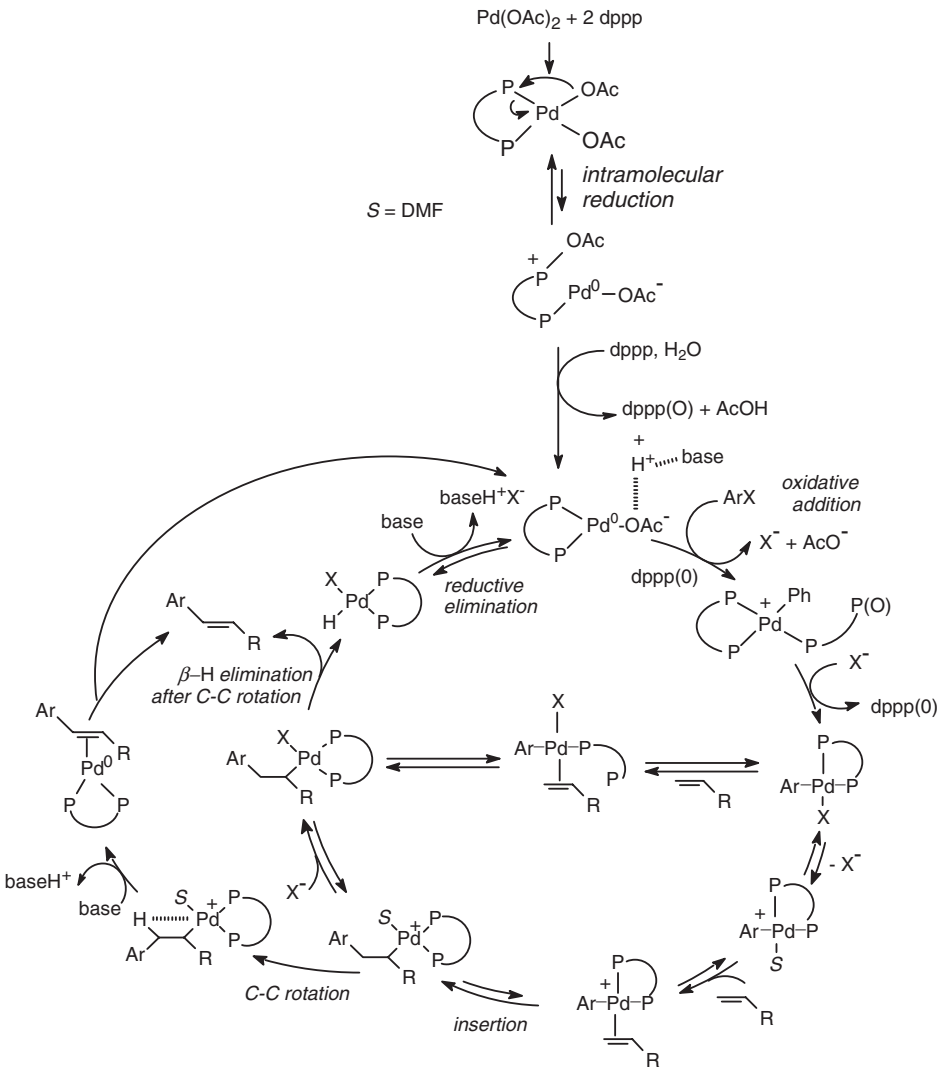


Scheme 1.36 *Mechanism of the Mizoroki–Heck reaction when the catalytic precursor is Pd(OAc)$_2$ associated with dppp: (i) when X′ = X = I, R = Ph, O-i-Bu (the formation of HPdS(dppp)$^+$ may be by-passed if the base is strong enough to deprotonate the agostic H in the σ-alkyl–PdS(dppp)$^+$ complexes, see Scheme 1.37); (ii) when acetate is used as base with X′ = I, X = OAc, R = Ph, O-i-Bu, CO$_2$Me.*

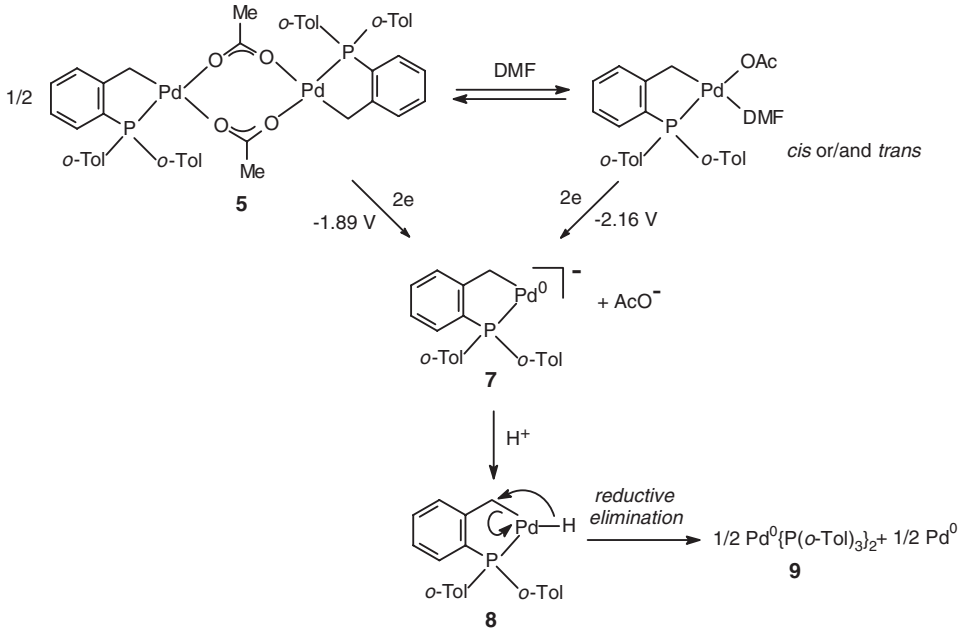
In Mizoroki–Heck reactions, in the absence of clearly identified reducing agent and due to the recovery of the monomeric *P*,*C*-palladacycle **6** at the end of a Mizoroki–Heck reaction performed from an aryl bromide, a catalytic cycle involving Pd^{II}/Pd^{IV} complexes was first proposed [27, 57]. DFT calculations have, however, established that the oxidative addition of iodobenzene with a Pd(II) complex is energetically not favoured at all [58]. Some Mizoroki–Heck reactions proceed with an induction period when the base is a tertiary amine [55b], but no induction period is observed when an acetate salt is used as a base [27, 55]. This is why the palladacycle **5** is often associated with an acetate salt used as base [27, 55a]. The induction period was explained by Beller and Riermeier [55b] as a slowly occurring reduction of the palladacycle **5** to give the active Pd(0) complex [Pd^0{P(*o*-Tol)$_3$}]. Even in the absence of any identified reducing agent, Böhm and Herrmann [59] have also proposed the reduction *in situ* of the palladacycle **5** to an anionic Pd(0) complex **7**, still ligated to the benzyl moiety of the ligand. The first step of the catalytic cycle would



Scheme 1.37 *Mechanism of the Mizoroki–Heck reaction when the catalytic precursor is $Pd(OAc)_2$ associated with dppp and when the base is not an acetate salt (e.g. base = NEt_3): X = I, R = CO_2Me.*

then be the classical oxidative addition of an aryl halide to a Pd(0) complex, as in a classical catalytic cycle involving Pd^0/Pd^{II} complexes.

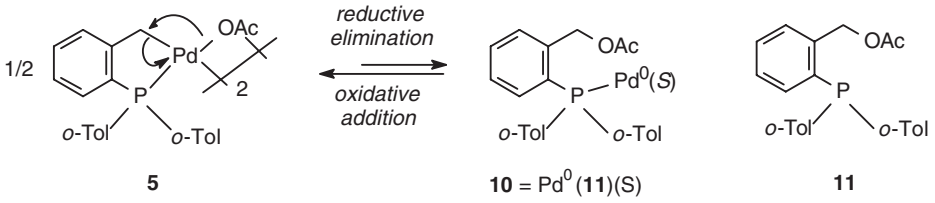
In 2005, upon investigation of the electrochemical properties of the palladacycle **5** in DMF, d'Orlyé and Jutand [28] showed that a Pd(0) complex (characterized by its oxidation peak at +0.2 V versus saturated calomel electrode (SCE)) is generated by the electrochemical reduction of **5** and its monomers in DMF (Scheme 1.38). However, the final Pd(0) species is not the electrogenerated complex **7** proposed by Böhm and Herrmann [59].



Scheme 1.38 *Electrochemical reduction of palladacycle **5** in equilibrium with monomers in DMF at 25 °C (peak potentials are measured versus SCE reference electrode).*

Instead, $Pd^0\{P(o\text{-Tol})_3\}_2$ (**9**) is formed upon fast protonation of **7** followed by reductive elimination from complex **8** (Scheme 1.38) [28]. Therefore, in DMF, the palladacycle **5** is reduced to a Pd^0 complex at a rather high negative potential that could be reached by zinc powder (Scheme 1.38). Such a strong reducing agent is, however, never present in Mizoroki–Heck reactions. No oxidation peak was detected when the cyclic voltammetry of **5** was performed directly towards oxidation potentials, establishing that a Pd(0) complex is not generated spontaneously from the palladacycle **5** in DMF at 25 °C.

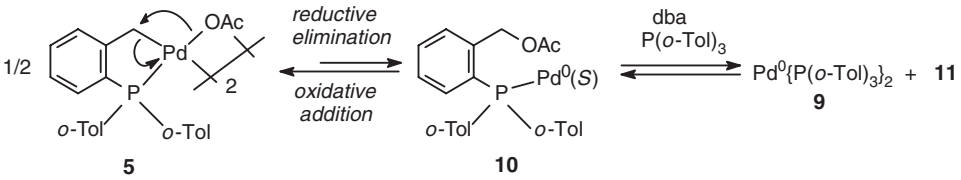
In 2005, d'Orlyé and Jutand [28] hypothesized that a Pd(0) complex might be generated *in situ* from the palladacycle **5** in an endergonic reductive elimination between the benzylic group attached to the Pd(II) centre and the *cis*-acetate ligand (Scheme 1.39). This reaction generates the monophosphine–Pd(0) complex **10** ligated by the new ligand **11** formed in the reductive elimination. The backward reaction in Scheme 1.39, an intramolecular oxidative



Scheme 1.39 *Formation of a Pd^0 complex by reductive elimination (S = solvent).*

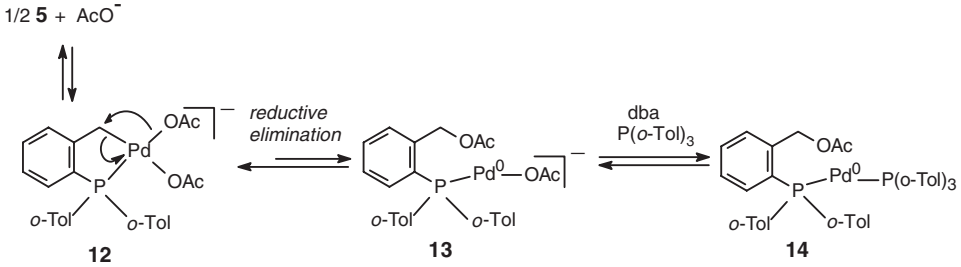
addition of the Pd(0) with the C—O bond of the *o*-benzylic acetate in complex **10**, must be very fast due to its intramolecular character. This is why the equilibrium in Scheme 1.39 would lie in favour of the palladacycle **5** at 25 °C. Consequently, the Pd(0) complex generated at low concentration in the endergonic reductive elimination could be detected (e.g. by an oxidation peak), provided the equilibrium in Scheme 1.39 is shifted towards its right-hand side by trapping the low-ligated Pd(0) complex **10** by additional ligands: P(*o*-Tol)$_3$, dba or AcO$^-$. Those additives have been selected because they cannot reduce the palladacycle **5** to a Pd(0) complex.

D'Orlyé and Jutand [28] have indeed shown that a Pd(0) complex is generated *in situ* from the palladacycle **5** after addition of dba and P(*o*-Tol)$_3$ in large excess at 80 °C in DMF; that is, in the absence of any reducing agents. This Pd(0) complex has been characterized by an oxidation peak (+0.19 V versus SCE) which disappears after addition of PhI, confirming *a posteriori* the formation *in situ* of a Pd(0) from **5** or its monomeric form in DMF. The oxidation peak potential characterizes the complex Pd^0{P(*o*-Tol)$_3$}$_2$ (**9**) formed from complex **10**, due to the large excess of P(*o*-Tol)$_3$ (Scheme 1.40) [28].



Scheme 1.40 *Formation of a detectable Pd(0) complex from* ***5*** *(*S = *DMF).*

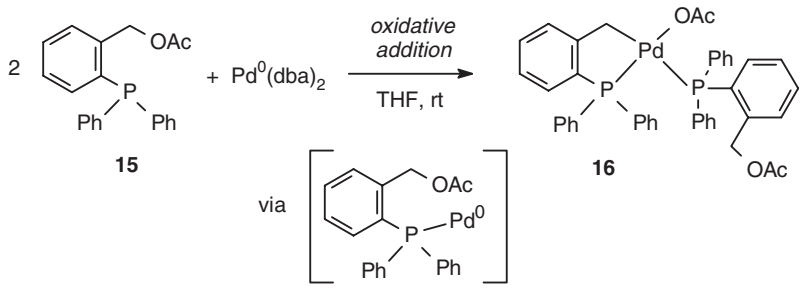
As mentioned above, acetate salts are often used as base in palladacycle-catalysed Mizoroki–Heck reactions [1j,s, 27, 55]. D'Orlyé and Jutand have established that an anionic monopalladacycle (**12**) is formed upon addition of excess *n*-Bu$_4$NOAc to **5** in DMF (Scheme 1.41). After further addition of a stoichiometric amount of P(*o*-Tol)$_3$ (P/Pd = 1) and excess dba [60], an oxidation peak is detected after 1 h at 80 °C, at a slightly less positive potential (+0.14 V versus SCE) than that obtained in the absence of acetate ions (see above). This oxidation peak disappears when the solution is cooled to 20 °C and appears again upon increasing the temperature to 60–80° C. It definitively disappears after addition of PhI, confirming that a Pd(0) complex has been generated



Scheme 1.41 *Formation of a detectable Pd(0) complex* ***14*** *from palladacycle* ***5*** *in the presence of acetate ions and P(*o*-Tol)$_3$ in DMF at 80 °C.*

in situ from the palladacycle **5** via the anionic complex **12** in the absence of any reducing agent (Scheme 1.41). The reversible reductive elimination has been shifted towards the formation of complex **14** by successive stabilization of the Pd(0) complex by acetate and P(*o*-Tol)$_3$ (Scheme 1.41) [28].

The oxidative addition of Pd^0(dba)$_2$ to PPh$_2$(*o*-benzyl acetate) (**15**) (a related but less-hindered ligand than **11**) generates a mononuclear *P*,*C*-palladacycle **16** (Scheme 1.42) [28, 61]. The cleavage of the benzyl–OAc bond of the ligand **15** by a Pd(0) complex by oxidative addition supports the idea that the formation of the Pd(0) complex **10** in Scheme 1.39 is, indeed, reversible [28].

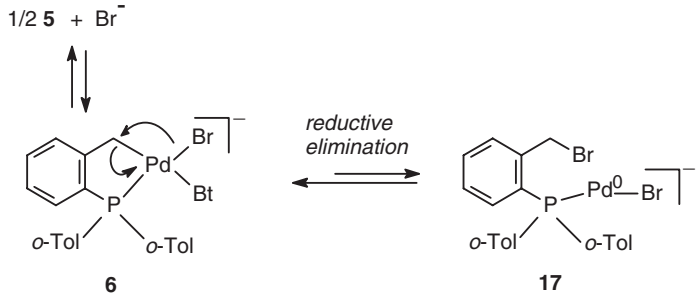


Scheme 1.42

Therefore, d'Orlyé and Jutand have established that the *P*,*C*-palladacycle **5** is a reservoir of a monophosphine–Pd(0) complex Pd^0{P(*o*-Tol)$_2$(*o*-benzyl–OAc)}(DMF) **10**, generated *in situ* by a reductive elimination between the OAc ligand and the *o*-benzyl moiety of the phosphine ligand in a reversible process. Such a reaction is favoured by acetate anions, often used as base in Mizoroki–Heck reactions, via the formation of an anionic monomeric *P*,*C*-palladacycle complex (**12**) ligated by acetate. This explains why no induction period is observed in Mizoroki–Heck reactions when NaOAc is used as base (see above) [27, 55]. This reversible formation of a Pd(0) complex ensures the stability of the *P*,*C*-palladacycle structure in Mizoroki–Heck reactions. Indeed, the anionic bromide-ligated monomeric palladacycle **6** has been observed by Herrmann *et al.* in the course of Mizoroki–Heck reactions performed from aryl bromides [27]. Such an anionic palladacycle is formed by reaction of **5** with bromide ions released in the catalytic reaction or voluntarily added. The complex **6** may undergo a reversible reductive elimination between the benzylic carbon and a bromide ligand to give the anionic Pd(0) complex **17** similar to **13** (Scheme 1.43).

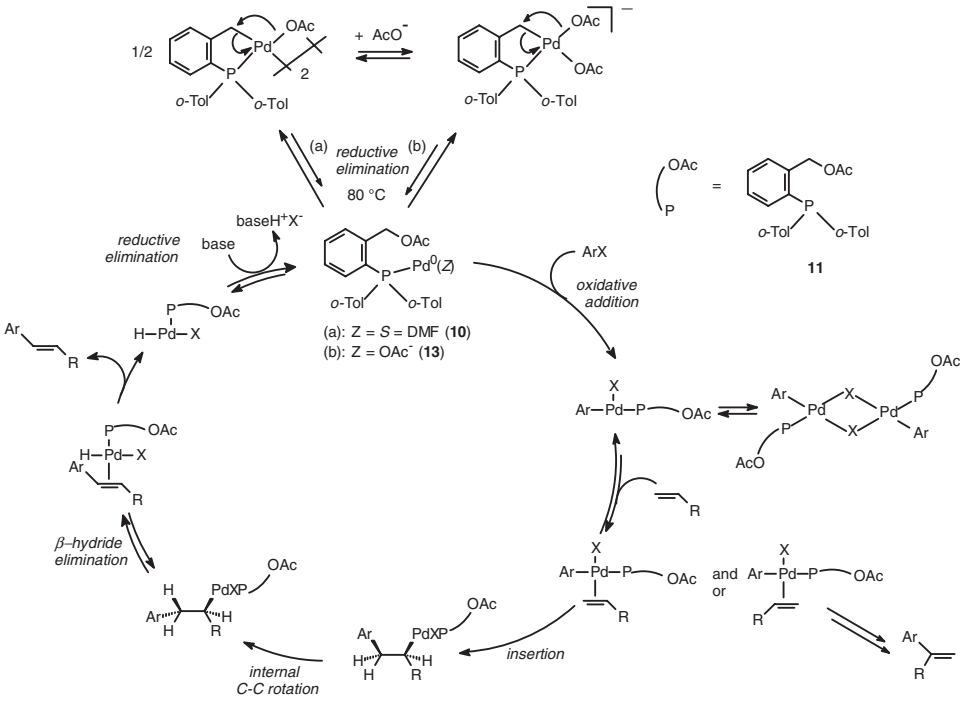
1.5.2 Catalytic Cycle

A catalytic cycle is proposed for Mizoroki–Heck reactions involving a *P*,*C*-palladacycle precursor based on the fact that a monoligated Pd(0) complex is formed from *P*,*C*-palladacycle precursors (see above). The structure of the Pd(0) complex **10** is close to that of Pd^0{P(*o*-Tol)$_3$} generated from Pd^0{P(*o*-Tol)$_3$}$_2$ as the minor but active species in oxidative additions of aryl bromides, as reported by Hartwig and Paul [62a]. The oxidative addition gives the dimeric complex [ArPd(μ-Br){P(*o*-Tol)$_3$}]$_2$ in equilibrium with the former T-shaped complex ArPdBr{P(*o*-Tol)$_3$} prone to react with a nucleophile [62b,c]. Such a mechanism must be valid for the Pd(0) complexes **10** or **13** generated *in situ* from the



Scheme 1.43

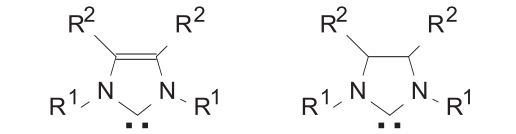
P,*C*-palladacycle precursors and ligated to the monophosphine **11** (Scheme 1.44). Kinetic data are still missing for most steps of the catalytic cycle [63]. The oxidative addition of aryl bromides is probably not rate determining, since the rate of the overall reaction is highly dependent on the structure of the alkene, as evidenced by competitive reactions of two different alkenes with the same aryl bromide in the presence of **5** [55a]. However, the alkene might also favour the reductive elimination in the palladacycle **5**, which slowly delivers the active Pd(0) complex into the catalytic cycle [60].



Scheme 1.44 *Mechanism for* P,C*-palladacycle-catalyzed Mizoroki–Heck reactions performed in DMF (route a) or in the presence of acetate ions as a base (route b).*

1.6 Mechanism of the Mizoroki–Heck Reaction when the Ligand is an *N*-Heterocyclic Carbene

N-Heterocyclic carbenes (NHCs, named Cb in the following, Chart 1.1) were introduced as ligands by Herrmann *et al.* [64] in their search to activate aryl chlorides or poorly reactive aryl bromides in Mizoroki–Heck reactions (for recent reviews, see [1p,q,s,t,w,x]). NHCs are indeed strong σ-donor and weak π-acceptor ligands [65] which make Pd(0) complexes more electron-rich and thus favour the oxidative addition of relatively unreactive aryl halides. C=C unsaturated NHCs have been introduced in Mizoroki–Heck reactions via a $PdI_2(Cb)_2$ precursor (R_1 = Me, R_2 = H in Chart 1.1, left) by Herrmann *et al.*, who observed an acceleration of the reactions upon addition of a reducing agent (hydrazine). This establishes that Pd(0) ligated by carbene(s) is the active species in the oxidative addition step [64].



C=C unsaturated NHC C-C saturated NHC

Chart 1.1

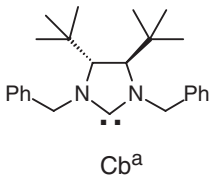
$PdX_2(Cb)_2$ (X = halide, acetate) precursors may be formed from a Pd(II) salt (e.g. $Pd(OAc)_2$) and *N*-heterocyclic azolium salts which are deprotonated into the NHC ligand [1p, 64, 66a–c]. They are also generated *in situ* when *N*-heterocyclic azolium salts are used as ionic liquid solvents [66d,e]. Isolated stable NHC-ligated Pd(0) complexes [67] are also used as catalysts in Mizoroki–Heck reactions [68].

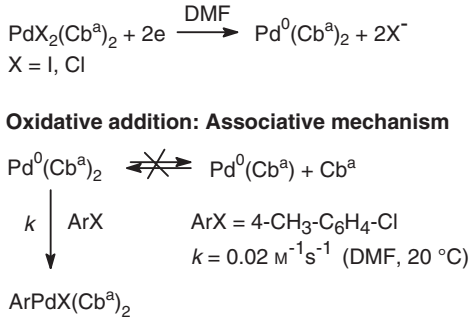
1.6.1 Oxidative Addition

The oxidative addition of aryl halides to $Pd^0(Cb)_2$ complexes has been reported and the complexes *trans*-$ArPdX(Cb)_2$ (Cb = *cyclo*-$C\{NR^1CR^2\}_2$, X = I, $R^1 = R^2$ = Me; X = Cl, R^1 = *t*-Bu, R^2 = H; Chart 1.1, left) formed in the reaction have been isolated and characterized [68a, 69, 70]. The aryl–palladium(II) complexes are always ligated by two carbene ligands irrespective of their bulkiness.

Kinetics data on the oxidative addition are scarce. In 2003, Roland and coworkers [71] used $PdX_2(Cb^a)_2$ (X = I, Cl) as an efficient precursor for Mizoroki–Heck reactions performed from aryl bromides at moderate temperatures (Scheme 1.45). Since $Pd^0(Cb^a)_2$ could not be isolated, its reactivity with aryl halides was followed by cyclic voltammetry, the transient $Pd^0(Cb^a)_2$ being generated in the electrochemical reduction of the precursors $PdX_2(Cb^a)_2$ in DMF (Scheme 1.45). The rate constants *k* of the oxidative addition of aryl halides to $Pd^0(Cb^a)_2$ have been determined (Table 1.3) [71].

In the late 2003, Caddick and coworkers [70] reported that the isolated $Pd^0(Cb^b)_2$, where Cb^b is much more bulky than Cb^a, reacts with 4-CH_3–C_6H_4–Cl via $Pd^0(Cb^b)$ in a dissociative mechanism (Scheme 1.46). The reactivity of $Pd^0(Cb^b)$ in the dissociative





Scheme 1.45

mechanism is controlled by the value of its rate constant k and its concentration, which is very low due to the endergonic equilibrium with $Pd^0(Cb^b)_2$ (see the value of K in Scheme 1.46): rate $= k[Pd^0(Cb^b)][4\text{-chlorotoluene}] = kK[Pd^0(Cb^b)_2][4\text{-chlorotoluene}]/[Cb^b]$. As a result, the overall reaction is quite slow and could be followed by ^1H NMR ($t_{1/2} \approx 24$ h when $[Pd^0] = [4\text{-chlorotoluene}] = 0.2$ M) [70].

DFT calculations reported by Green *et al*. [72] in 2005 on Pd(0) complexes ligated by two C=C unsaturated carbenes close to Cb^b support the dissociative mechanism with this assumption: the bulkier the substituent on the N atoms is, the lower the dissociation energy of the biscarbene–Pd(0) complex is.

In 2006, Jutand and coworkers [73] extended their former work of 2003 to the reactivity of the electrogenerated $Pd^0(Cb^a)_2$ with aryl chlorides. The reactions take place at 20 °C in DMF (Scheme 1.45, Table 1.3). As in all oxidative additions [6c], the following reactivity orders have been established:

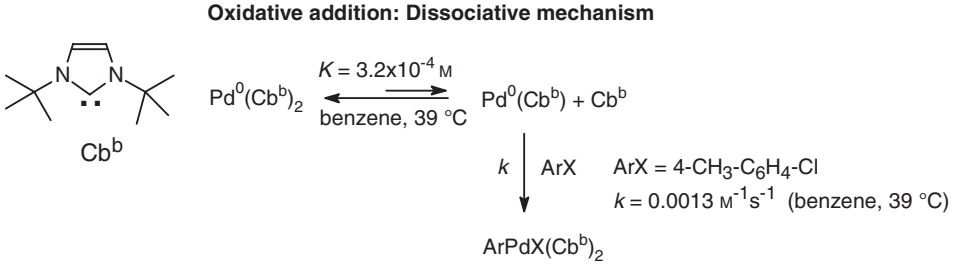
$$PhI > PhBr > PhCl$$
$$4-CF_3—C_6H_4—Cl > C_6H_5—Cl > 4-CH_3—C_6H_4—Cl$$

Jutand and coworkers [73] have established that $Pd^0(Cb^a)_2$ is the reactive species in an associative mechanism (Scheme 1.45); this is in contrast to $Pd^0(Cb^b)_2$, which reacts via $Pd^0(Cb^b)$ in a dissociative mechanism (Scheme 1.46) [70]. This is rationalized by steric factors. The stable Cb^b carbene is bulky and thus prompted to dissociation from $Pd^0(Cb^b)_2$ [72]. Conversely, the ligand Cb^a is less stable and less bulky than Cb^b, as evidenced by

Table 1.3 *Rate constants* k *of the oxidative addition of aryl halides to Pd(0) complexes electrogenerated from Pd(II) precursors in DMF at 20 °C (Scheme 1.45)*

	k (M^{-1} s^{-1})				
Pd(0) complex	PhI	PhBr	PhCl	4-CH_3—C_6H_4—Cl	4-CF_3—C_6H_4—Cl
$Pd^0(Cb^a)_2$	>1180	1180	0.13	0.02	0.35
$Pd^0(Cb^a)(PPh_3)$	830	2	n.d.	n.d.	n.d.

n.d.: not determined.



Scheme 1.46

the X-ray structure of the parent complex $PdI_2(Cb^a)_2$ [71]. Therefore, $Pd^0(Cb^a)_2$ is less inclined to dissociation than $Pd^0(Cb^b)_2$. Interestingly, comparison of the reactivity of 4-chlorotoluene with $Pd^0(Cb^a)_2$ and $Pd^0(Cb^b)_2$ shows that $Pd^0(Cb^a)_2$, which reacts via the associative mechanism (Scheme 1.45), is more reactive than $Pd^0(Cb^b)_2$, which reacts via $Pd^0(Cb^b)$ in the dissociative mechanism (Scheme 1.46). Moreover, when comparing their respective rate constants k, one sees that $Pd^0(Cb^a)_2$ ($k = 0.02\ \text{M}^{-1}\ \text{s}^{-1}$, 20 °C, Scheme 1.45) is even more reactive than $Pd^0(Cb^b)$ ($k = 0.0013\ \text{M}^{-1}\ \text{s}^{-1}$, 39 °C, Scheme 1.46) at identical concentrations of Pd(0) and 4-chlorotoluene [73].

$$Pd^0(Cb^a)_2 > Pd^0(Cb^b) \gg Pd^0(Cb^b)_2$$

In other words, the involvement of a monoligated $Pd^0(Cb)$ as the active species is not a guarantee for a fast oxidative addition, because $Pd^0(Cb)$ is always generated at low concentration in its endergonic equilibrium with the nonreactive $Pd^0(Cb)_2$ complex.

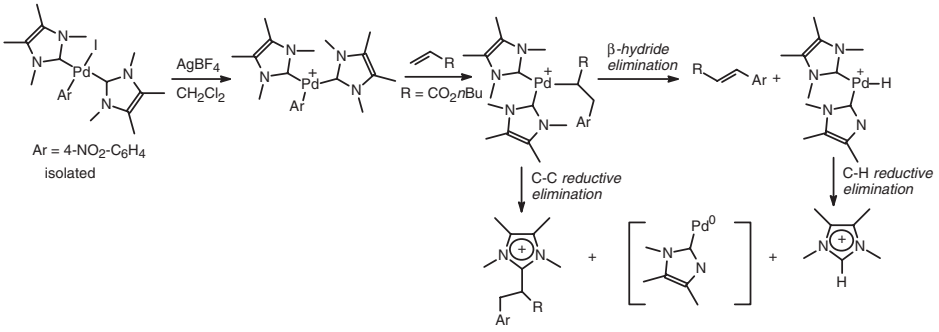
Therefore, the structure of the reactive Pd(0) in oxidative addition ($Pd^0(Cb)$ versus $Pd^0(Cb)_2$) is governed by the bulk of the carbene ligand; but the reactivity is not necessarily controlled by the structure of the reactive species, since a bis-ligated $Pd^0(Cb)_2$ (e.g. Cb = Cb^a) may be even more reactive than a monoligated $Pd^0(Cb')$ (e.g. Cb′ = Cb^b). Electronic factors must also be taken into consideration, C—C saturated carbenes (as Cb^a) being stronger σ-donors than C=C unsaturated carbenes (as Cb^b) [65g].

The mixed carbine–phosphine $Pd^0(Cb^a)(PPh_3)$ generated in the electrochemical reduction of $PdI_2(Cb^a)(PPh_3)$ also reacts in an associative mechanism and is less reactive than $Pd^0(Cb^a)_2$ (Table 1.3) [71, 73], showing that the carbene Cb^a is indeed much more electron donating than PPh_3. However, $Pd^0(Cb^a)(PPh_3)$ is much more efficient than $Pd^0(Cb^a)_2$ in Mizoroki–Heck reactions performed from PhBr [71], suggesting that the oxidative addition is not rate determining.

1.6.2 Complexation/Insertion of the Alkene

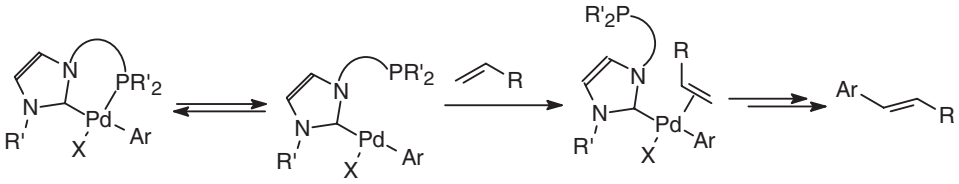
Because of the lack of kinetic data, the mechanism of the insertion of the alkene is currently speculative. The alkene might react with *trans*-$ArPdX(Cb)_2$ either via the cationic complex $ArPd(Cb)_2^+$ (after dissociation of X^-) or via the neutral ArPdX(Cb) (after dissociation of one Cb). DFT calculations by Rösch and coworkers [74] in 1998, reinforced by experimental work by Cavell and coworkers [68a] in 1999 on the comparative reactivity of CH_2=CH—CO_2-*n*-Bu with isolated *trans*-$ArPdI(Cb)_2$ and $ArPd(Cb)_2^+$ (generated

in situ by halide abstraction in dichloromethane), led to the conclusion that the alkene reacts faster with the cationic *trans*-ArPd*S*$(Cb)_2^+$ than with *trans*-ArPdI$(Cb)_2$, suggesting that the dissociation of the strong σ-donor Cb is thermodynamically less favoured (Scheme 1.47). However, the reaction involving the cationic complex gives rise to by-products formed by reductive elimination of the carbene ligand with the alkyl group or with the hydride, giving imidazoliums (Scheme 1.47) [68a].



Scheme 1.47 *Reaction of an alkene with a cationic ArPd(Cb)$_2^+$ and subsequent by-reactions (the precomplexation of the alkene to the cationic ArPd(Cb)$_2^+$ is omitted).*

DFT calculations by Rösch and coworkers [74] showed that for PhPdCl(P^Cb) complexes, where the bidentate ligand P^Cb is a monophosphine linked to an NHC, the reaction with an alkene proceeds via dissociation of the more labile phosphine; that is, via a neutral Cb-linked ArPdX complex (Scheme 1.48). Later on, bidentate P^Cb ligands generated *in situ* from phosphine–imidazolium salts proved to be efficient in Mizoroki–Heck reactions employing aryl bromides – even deactivated ones, as pioneered by Nolan and coworkers [1q, 75]. Interestingly, the DFT calculations have paved the way to fruitful experiments.

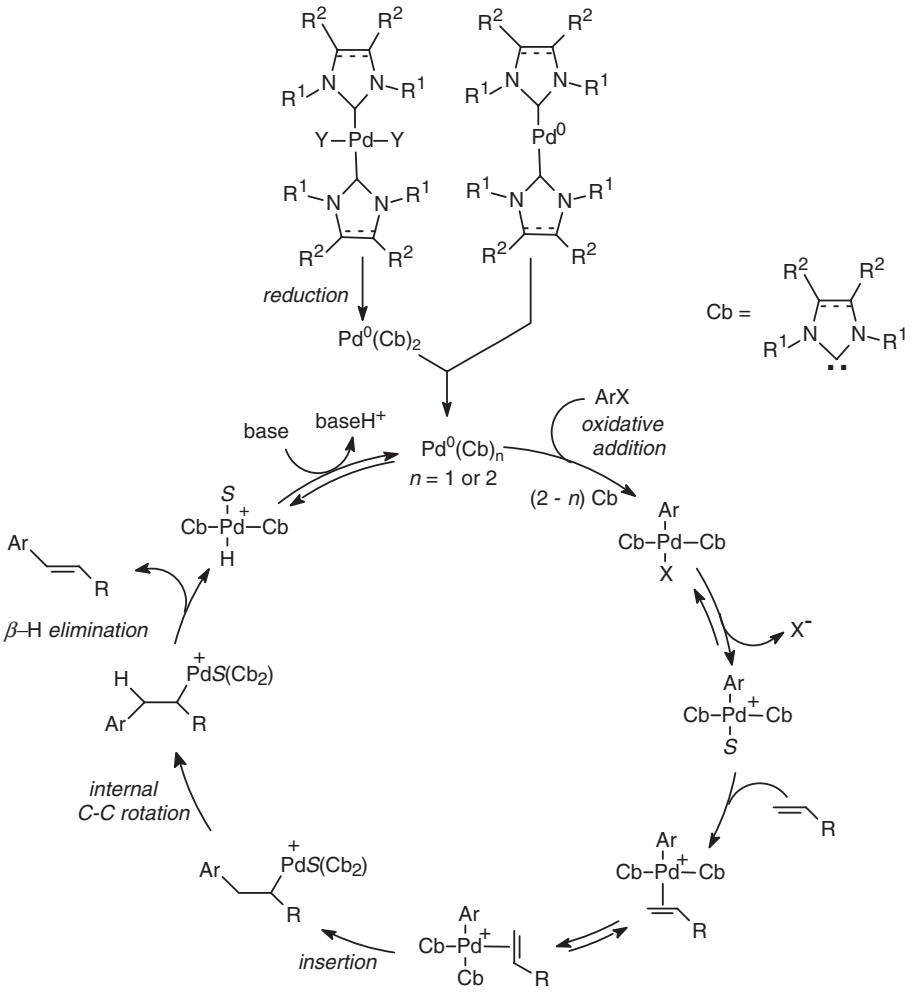


Scheme 1.48

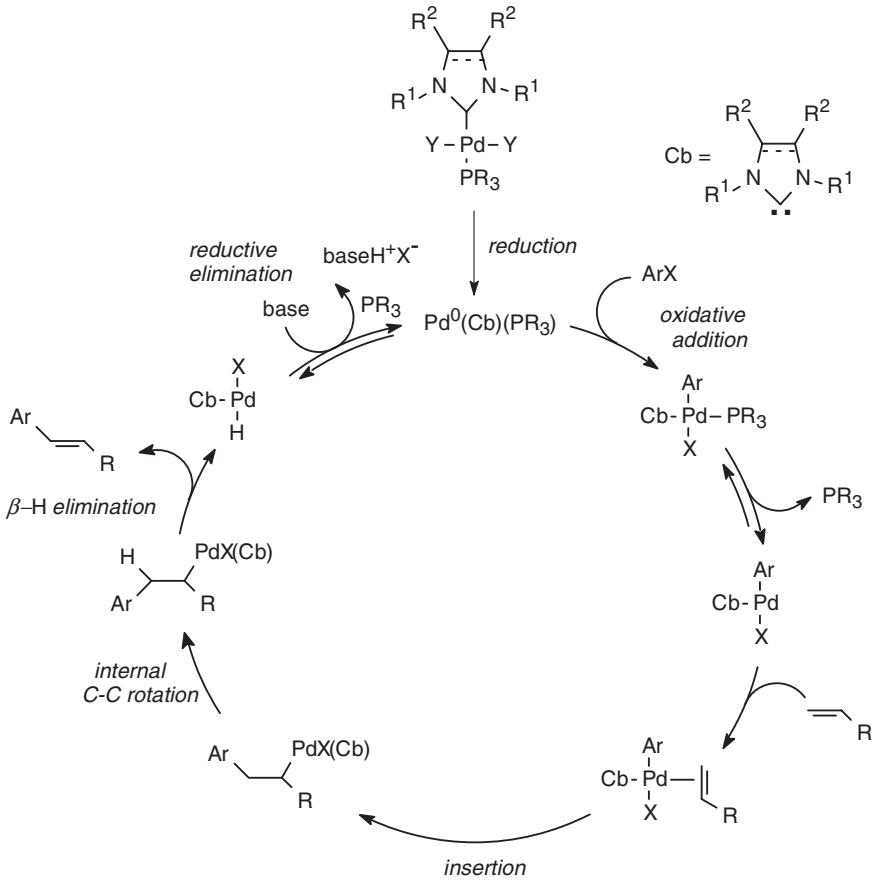
It appears reasonable to predict that ArPdX(Cb)(PR_3) complexes generated in the oxidative addition of ArX to Pd^0(Cb)(PR_3) would dissociate to ArPdX(Cb), which reacts with the alkene. Such a dissociation of the phosphine must be even easier than the intramolecular dissociation of the phosphine in the bidentate P^Cb ligand proposed above. This is probably why mixed complexes Pd^0(Cb)(PR_3) are more efficient than $Pd^0(Cb)_2$ in Mizoroki–Heck reactions performed from aryl bromides [71, 76], even if they are less reactive than $Pd^0(Cb)_2$ in the oxidative addition. Indeed, the high stability of the Cb–Pd(II) bond combined with the easy dissociation of the phosphine in ArPdX(Cb)(PR_3) favours the complexation/insertion of the alkene.

1.6.3 Catalytic Cycles

The above considerations are summarized in three individual catalytic cycles: the *ionic* mechanism catalysed by a Pd(0) coordinated to one or two C—C saturated or C=C unsaturated NHC monocarbenes (Scheme 1.49); the *neutral* mechanism catalysed by mixed Pd(0) complexes coordinated to one C—C saturated or C=C unsaturated NHC monocarbene and one phosphine (Scheme 1.50); and the *neutral* mechanism catalysed by Pd(0) coordinated to a bidentate P^Cb ligand (Scheme 1.51).



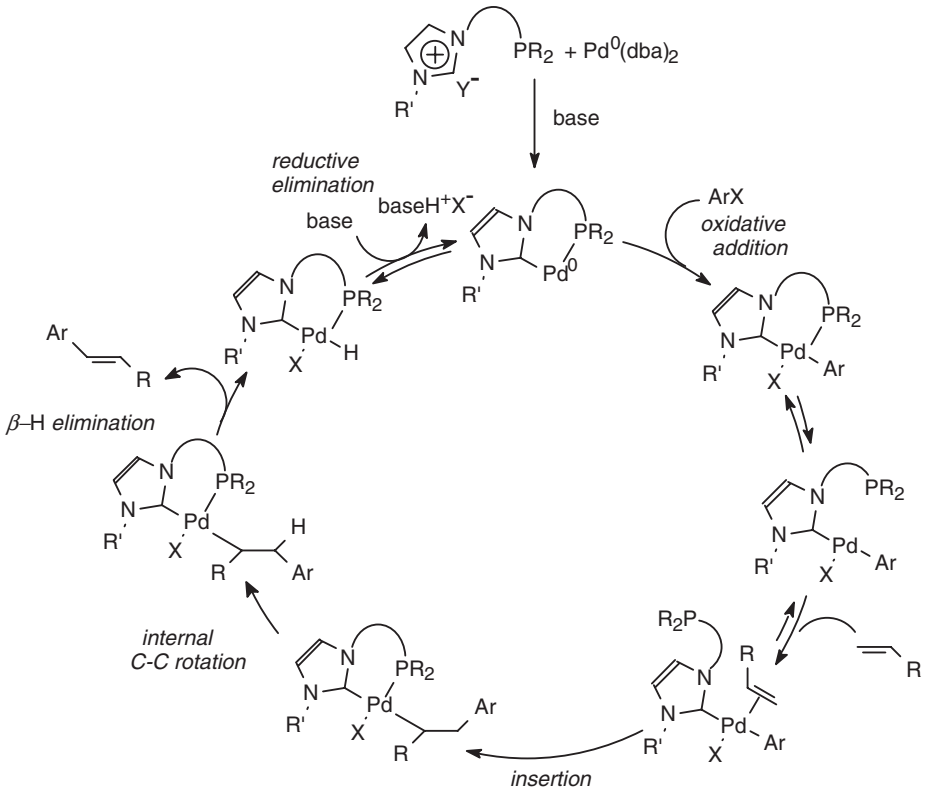
Scheme 1.49 Ionic *mechanism for Mizoroki–Heck reactions catalysed by a Pd(0) coordinated to one or two C—C saturated or C=C unsaturated* N*-heterocyclic monocarbenes (only one way for the coordination of the alkene is presented). The reactive species is* $Pd^0(Cb)$ *for a bulky carbene and* $Pd^0(Cb)_2$ *for a nonbulky carbene. The aryl–palladium complex formed in the oxidative addition is always ligated by two Cb ligands delivered by the Pd(0) or Pd(II) precursor even if* $Pd^0(Cb)$ *is the reactive species.*



Scheme 1.50 Neutral *mechanism for Mizoroki–Heck reactions catalysed by mixed Pd(0) complexes coordinated to one C—C saturated or C═C unsaturated* N*-heterocyclic monocarbene and one phosphine (only one orientation of the alkene is presented).*

1.7 Mechanism of the Mizoroki–Heck Reaction when the Ligand is a Bulky and Electron-Rich Monophosphine

The introduction of *P*,*C*-palladacycles [27, 55a] or NHC-ligated palladium complexes by Herrmann *et al*. [64] has permitted the use of activated aryl chlorides (substituted by EWGs) in Mizoroki–Heck reactions. However, the reactions were performed at high temperatures (120–160 °C) and chlorobenzene or nonactivated aryl chlorides (substituted by EDGs) were not reactive [1r,y]. The further significant improvement was the introduction of bulky and electron-rich phosphines by Littke and Fu [77] in association with the precursor $Pd^0{}_2(dba)_3$. Among them, tri-*tert*-butylphosphine, P-*t*-Bu_3, is the best ligand for reactions of nonactivated aryl chlorides under mild conditions: P-*t*-$Bu_3 \gg PCy_3$ (Cy = cyclohexyl) [77a]. The efficiency of the Mizoroki–Heck reactions involving P-*t*-Bu_3 is, however, very dependent on the base. By replacing Cs_2CO_3 by Cy_2NMe, the Mizoroki–Heck reactions



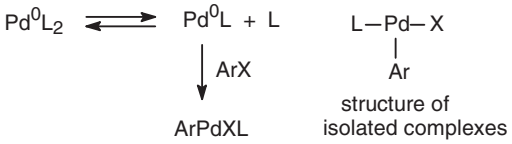
Scheme 1.51 Neutral *mechanism for Mizoroki–Heck reactions catalysed by Pd(0) coordinated to a bidentate P^Cb ligand.*

from activated aryl chlorides are performed at room temperature, whereas nonactivated or hindered aryl chlorides are converted at 100–120 °C [77b]. In the same phosphine series, changing one or two *t*-Bu groups, as in Fc′–P-*t*-Bu_2 (Fc′ = aryl-substituted ferrocenyl) or $(Ad)_2$P-*t*-Bu (Ad = adamantyl), namely increasing the bulk of the phosphine, allows Mizoroki–Heck reactions with nonactivated aryl chlorides (NaOAc as base at 110 °C [78] and K_3PO_4 as base at 110 °C [79] respectively).

1.7.1 Oxidative Addition

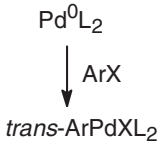
Barrios-Landeros and Hartwig [80a] have reported the mechanism of the oxidative addition of aryl bromides with Pd(0) complexes ligated by bulky electron-rich phosphines such as Pd^0(Fc′–P-*t*-Bu_2)$_2$ (Fc′ = aryl-substituted ferrocenyl). All Pd(0) complexes are found to react via a monophosphine complex Pd^0L in a dissociative mechanism, leading to the monophosphine T-shaped complex ArPdXL which may be stabilized by a weak agostic Pd–H bond (H from the ligand) [80b,c] (Scheme 1.52). The mechanism of the oxidative addition of PhBr to Pd^0(P-*t*-Bu_3)$_2$ (P-*t*-Bu_3: cone angle 182°, pK_a = 11.4) is not reported,

but the T-shaped structure of the complex PhPdBr(P-*t*-Bu_3) formed in the oxidative addition suggests that the reaction proceeds via the dissociative mechanism of Scheme 1.52 [80c]. The reaction of aryl chlorides is more problematic. The oxidative addition of PhCl with Pd^0(Fc′–P-*t*-$Bu_2)_2$ proceeds by the dissociative mechanism of Scheme 1.52 [80a], whereas no reaction occurs with Pd^0(P-*t*-$Bu_3)_2$ [80c]. However, evidence for the reactivity of Pd^0(P-*t*-Bu_3) with PhCl has been established in oxidative additions performed in the presence of bases [80d]. This suggests that the concentration of Pd^0(P-*t*-Bu_3) in its equilibrium with Pd^0(P-*t*-$Bu_3)_2$ must be very low and that decreasing the ratio P-*t*-Bu_3/Pd should be beneficial for catalytic reactions. Indeed, Littke and Fu [77b] have observed that, in a Mizoroki–Heck reaction performed from 4-chloroacetophenone and styrene in the presence of Cy_2NMe as base (i.e. in conditions where the oxidative addition is rate limiting), the catalytic systems {1.5% $Pd^0{}_2(dba)_3$ + 3% P-*t*-Bu_3} or {1.5% Pd^0(P-*t*-$Bu_3)_2$ + 0.75% $Pd^0{}_2(dba)_3$} for which the ratio Pd/P = 1 give the same conversion of 30% after the same reaction time, whereas using 3% of Pd^0(P-*t*-$Bu_3)_2$ leads to only 2% conversion. When the precursor is $Pd^0{}_2(dba)_3$ associated with P-*t*-Bu_3 so that Pd/P = 1, the major complex Pd^0(dba)(P-*t*-Bu_3) must be formed, which dissociates to Pd^0(P-*t*-Bu_3) more easily than Pd^0(P-*t*-$Bu_3)_2$ does [81].



Scheme 1.52 *Dissociative mechanism for the oxidative addition.*

When less bulky ligands are involved, such as PCy_3 (cone angle 170°, pK_a = 9.7), the complex $Pd^0(PCy_3)_2$ reacts with aryl halides, including chlorobenzene, in an associative mechanism [82a, Brown and Jutand, in preparation] to give the bis-phosphine complex ArPdX$(PCy_3)_2$ [82] (Scheme 1.53). Therefore, the structure of the aryl–palladium(II) complex, ArPdXL versus $ArPdXL_2$, is controlled by steric factors rather than by electronic factors.



Scheme 1.53 *Associative mechanism for the oxidative addition (L = PCy_3, X = I, Br, Cl).*

1.7.2 Complexation/Insertion of the Alkene

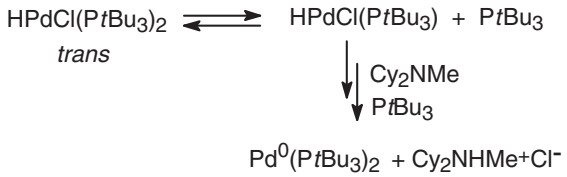
The reactivity of alkenes with isolated ArPdXL (L = P-*t*-Bu_3) complexes has not been investigated. The coordination of such 14-electron complexes by the alkene should not be rate limiting. However, the phosphine and the halide sit in a *trans* position in isolated

ArPdXL complexes (Scheme 1.52) [80c]. If that structure is maintained in solution, then the coordinated alkene and the aryl group will be *trans* related. This does not favour the alkene insertion, which requires an isomerization prior to insertion (see 1.7.4).

1.7.3 Role of the Base in the Recycling of the Pd(0) Complex

Investigation of the hydridopalladium complex formed in the β-hydride elimination step by Hill and Fu [83] in 2004 provided mechanistic insights for the first time on its key involvement in the success of Mizoroki–Heck reactions performed from aryl chlorides. With Cs_2CO_3 as base, HPdCl(P-*t*-$Bu_3)_2$ was detected by ^{31}P NMR spectroscopy (first identification of a hydridopalladium in the course of a Mizoroki–Heck reaction); in contrast, only Pd^0(P-*t*-$Bu_3)_2$ was observed with Cy_2NMe as base, not the hydridopalladium complex. This explains why Cy_2NMe is more efficient than Cs_2CO_3 for Mizoroki–Heck reactions performed from aryl chlorides, because it is more effective for the regeneration of the Pd(0) catalyst from HPdCl(P-*t*-$Bu_3)_2$.

The kinetics of the reaction of *trans*-HPdCl(P-*t*-$Bu_3)_2$ with Cy_2NMe leading to Pd^0(P-*t*-$Bu_3)_2$ was investigated by Hill and Fu [83]. The overall reaction is made irreversible in the presence of a large excess of amine, as in catalytic reactions. The formation of the Pd(0) complex is inhibited by addition of P-*t*-Bu_3, which is consistent with an initial dissociation of one P-*t*-Bu_3 prior reductive elimination (Scheme 1.54) [83].

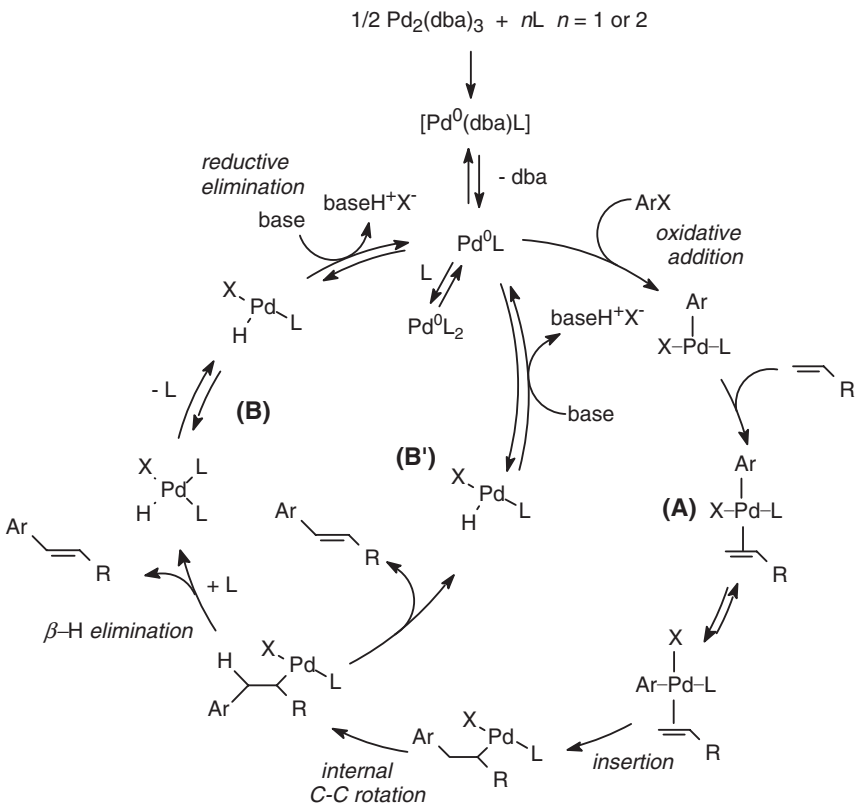


Scheme 1.54

Crystallization of HPdCl($PR_3)_2$ (R = *t*-Bu or Cy) reveals that the P–Pd–P angle is 161° in the bent HPdCl(P-*t*-$Bu_3)_2$ but 180° in HPdCl($PCy_3)_2$, which is thus less prone to reductive elimination [83]. This explains why, when using the same base, P-*t*-Bu_3 is more efficient than PCy_3 for Mizoroki–Heck reactions performed from aryl chlorides [77].

1.7.4 Catalytic Cycle

The efficiency of bulky and electron-rich phosphines in Mizoroki–Heck reactions seems to be due to their ability to generate monophosphine–Pd(0) or –Pd(II) complexes in each step of the catalytic cycle (Scheme 1.55). Steric factors are probably more important than electronic factors. One sees from Fu's studies that the last step of the catalytic cycle in which the Pd(0) complex is regenerated in the presence of a base may be rate determining. The role of this last step has been underestimated for a long time. Provided this step is favoured (e.g. with P-*t*-Bu_3 as ligand and Cy_2NMe as base), the oxidative addition of aryl chlorides would appear to be rate determining. However, Mizoroki–Heck reactions performed from the same aryl chloride with the same Pd(0) catalyst and same base but



Scheme 1.55 *Mechanism of Mizoroki–Heck reactions performed from ArCl when L = P-t-Bu$_3$ (only one orientation of the alkene is presented). (A) + (B): catalytic cycle when* n = *2; (A) + (B′) catalytic cycle when* n = *1.*

with different alkenes (e.g. styrene versus methyl acrylate) require different reaction times and temperatures incompatible with a rate-determining oxidative addition [77a].

1.8 Conclusion

The Mizoroki–Heck reaction is a subtle and complex reaction which involves a great variety of intermediate palladium complexes. The four main steps proposed by Heck (oxidative addition, alkene insertion, β-hydride elimination and reductive elimination) have been confirmed. However, they involved a considerable number of different Pd(0) and Pd(II) intermediates whose structure and reactivity depend on the experimental conditions, namely the catalytic precursor (Pd(0) complexes, $Pd(OAc)_2$, palladacycles), the ligand (mono- or bis-phosphines, carbenes, bulky monophosphines), the additives (halides, acetates), the aryl derivatives (ArX, ArOTf), the alkenes (electron-rich versus electron-deficient ones), which may also be ligands for Pd(0) complexes, and at least the base, which can play a

multiple role as well. The efficiency and regioselectivity of Mizoroki–Heck reactions will only be optimal after finely balancing those parameters.

Depending on the experimental conditions, the catalytic cycles may involve: (i) Pd nanoparticles, anionic tri-ligated $Pd^0L_2(OAc)^-$ (L = monophosphine or L_2 = bidentate bisphosphine complexes), neutral Pd^0L_2 (L = carbene, monophosphine) or monoligated Pd^0L (L = bulky phosphine, bulky carbene); (ii) neutral $ArPd^{II}XL_2$ (X = halide or acetate) or cationic $ArPd^{II}SL_2{}^+$ complexes (L = monophosphine, monocarbene or L_2 = bidentate bisphosphine), T-shaped complex ArPdXL (L = bulky phosphines); (iii) $HPdClL_2$ or HPdClL (L = bulky monophosphine) complexes, and so on.

Kinetic data, however, are still missing for most steps which follow the oxidative addition for the precursors or ligands recently introduced in Mizoroki–Heck reactions (palladacycles, bulky phosphines and carbenes).

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