Variations on a theme—recent developments on the mechanism of the Heck reaction and their implications for synthesis
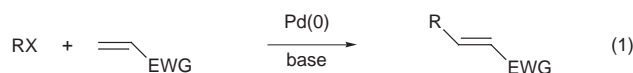
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The Heck reaction has been used extensively over the past 30 years for the elaboration of alkenes. Although many examples have been published in the literature it is only in the last few years that detailed mechanistic studies have been undertaken and a clearer understanding of the active species has emerged. This review will examine the implications of recent details on the mechanism of the Heck reaction using both traditional and non-traditional catalytic systems, highlight mechanistic details which must be updated in textbooks and summarise the protocols which a practising chemist might use to perform a successful Heck coupling.

1 Introduction

The arylation and alkenylation of alkenes under the influence of a palladium catalyst, commonly referred to as the Heck reaction, has been extensively exploited by synthetic chemists since its debut in the late 1960's.[1] A traditional Heck coupling was based on an aryl iodide or bromide as the electrophilic partner and a terminal alkene as the nucleophilic partner [eqn. (1), R = aryl, vinyl and X = I, Br]. The initial promise of a convenient method for carbon–carbon bond formation was only realised satisfactorily for terminal alkenes possessing an electron withdrawing group (for example, EWG = CO_2R, CN, Ph).

$$RX \quad + \quad \overset{}{=}\!\!\diagup_{EWG} \quad \xrightarrow[\text{base}]{\text{Pd(0)}} \quad \overset{R}{\diagup}\!\!=\!\!\diagdown_{EWG} \qquad (1)$$

The regiochemistry found for such transformations was consistent with carbon–carbon bond formation at the least

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hindered terminus of the alkene, much like in a Michael addition.[2] The stereochemistry of addition (discussed in more detail below) usually delivered a *trans* disubstituted alkene. The formation of regioisomers arose as a major problem for electronically neutral alkenes or those substituted with an electron donating group (such as OR or NR_2).[2] After considerable experimentation with a variety of ligands, palladium sources, solvents and additives many of the disadvantages associated with the traditional Heck conditions have been alleviated and we now have a convenient methodology for the construction of complex, multifunctional molecules. The key to using the Heck reaction as a crucial step in synthetic endeavours is to identify the class of Heck reaction in terms of both the type of alkene (whether electron donating or electron withdrawing) and the electrophile (whether a halide or a trifluoromethanesulfonate is the leaving group) and then select the most appropriate conditions in order to maximise the conversion. Various aspects of the Heck reaction have been reviewed in recent years including an extensive compilation of recent applications to the synthesis of complex natural products and cascade processes,[2] the use of the intramolecular Heck reaction for the construction of quaternary centres,[3,4] the intramolecular asymmetric Heck reaction[5] and a detailed summary of mechanistic details for the Heck reaction under a variety of conditions.[6]

In view of this plethora of excellent reviews why attempt another catalogue of past achievements in the area? This review will not be encyclopaedic but concentrate on the implications of recently published details on the mechanism of the Heck reaction using both traditional and non-traditional catalytic systems, highlight mechanistic details which must be updated in textbooks and summarise the protocols which a practising chemist might use to perform a successful Heck coupling.

2 Traditional mechanism proposed for the Heck reaction

We begin this excursion by reviewing the traditional mechanism for a Heck transformation, namely an aryl or vinyl halide (RX where X = Br, I) coupling with an acrylate (CH_2=CHEWG) under the influence of either $Pd(OAc)_2$ with added L, or $PdCl_2L_2$ or PdL_4 [where L is a tertiary phosphine ligand such as PPh_3 or P(*o*-tolyl)$_3$] as summarised in Scheme 1. Although the general features of this mechanism are still retained in recent proposals, the exact nature of the catalytically active species and the influence of associated ligands have been considerably modified.

The traditional mechanism proposes that, irrespective of the nature of the palladium precursor, the active catalytic unit is the coordinately unsaturated, 14 electron species PdL_2.[2] This would seem reasonable since PdL_2 is electron rich and nucleophilic in character and has vacant sites so that the organic electrophile RX can undergo oxidative addition to give the known *trans*-$RPdXL_2$ (**1**) intermediate in which the R group (aryl or vinyl) is σ-bonded to the Pd(II). The *trans* isomer (**1**) is formed by an isomerization of the thermodynamically less stable *cis* isomer. A vacant site must now be created to accommodate and activate

Scheme 1

base•HX

base → PdL$_2$ ← RX
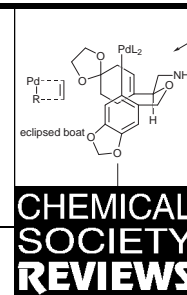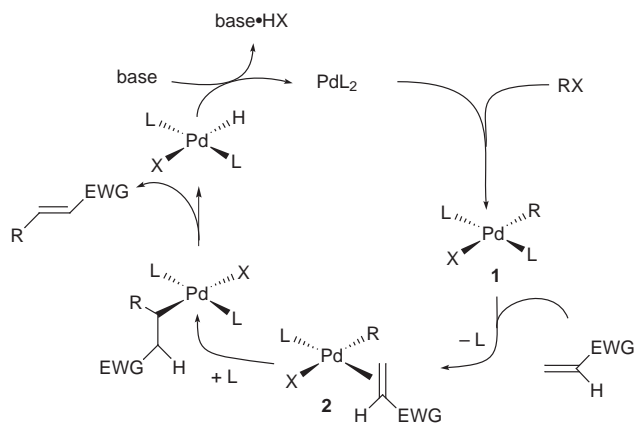
Scheme 1

the alkene, and for monodentate L this is usually assumed to be the phosphine, so that a neutral RPdXL(CH$_2$=CHEWG) (**2**) species is formed. The coordinated alkene then undergoes *syn* addition to form an unstable σ-bonded complex, which will rotate around the carbon–carbon bond so that the palladium and β-hydrogen are *syn* coplanar, and β-hydride elimination takes place to generate the observed *trans* substituted alkene and the catalytically inactive HPdXL$_2$ as outlined in Scheme 2. The
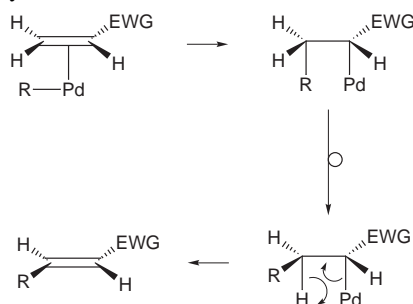
Scheme 2

base, which must be present to enact a successful catalytic cycle, reduces the HPdXL$_2$ to regenerate PdL$_2$ and the whole cycle repeats (Scheme 1). This mechanism served adequately for many years and rationalised the regio- and stereochemistry of the substituted alkene product and the need for stabilising ligands around the palladium.
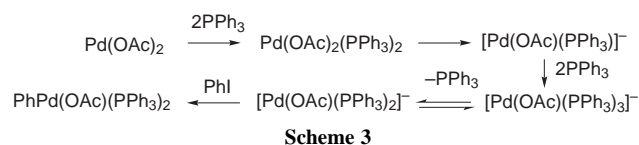
This mechanism does not rationalise many of the ligand and solvent effects which have been reported over the past decade, nor does it explain the marked accelerating effects observed for certain additives. It is worth detailing some of these recent insights into the various steps of the Heck reaction and how these have lead to new transformations, some of which were impossible with traditional Heck conditions.

3 Recent mechanistic details for the Heck reaction

3.1 Pd(OAc)$_2$ and PPh$_3$

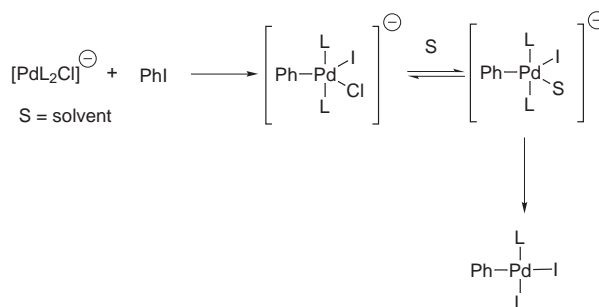A common catalyst combination for the traditional Heck reaction is Pd(OAc)$_2$ and 2–4 equivalents of PPh$_3$.[2] In the presence of the alkene an oxidation–reduction sequence was proposed which eventually delivered the proposed catalytically active species Pd(PPh$_3$)$_2$.[1] Recent examination of the stoichiometric reaction of polymeric Pd(OAc)$_2$ with PPh$_3$ has shown that an immediate transformation takes place in polar solvents such as dimethylformamide (DMF) with formation of Pd(PPh$_3$)$_2$(OAc)$_2$.[7] This Pd(II) substrate spontaneously forms [PdL$_n$(OAc)]$^-$ (n = 2, 3) as the reduced partner in an overall redox process. Complex [Pd(PPh$_3$)$_2$(OAc)]$^-$ is formally coordinately unsaturated and highly nucleophilic, two of the characteristics required for a rapid oxidative addition of RX. [Pd(PPh$_3$)$_2$(OAc)]$^-$ has been shown to undergo a rapid reaction with iodobenzene to give the oxidative addition product

PhPd(PPh$_3$)$_2$(OAc) and not the expected (and often proposed) PhPd(PPh$_3$)$_2$I (Scheme 3).[7]

Pd(OAc)$_2$ $\xrightarrow{\text{2PPh}_3}$ Pd(OAc)$_2$(PPh$_3$)$_2$ ⟶ [Pd(OAc)(PPh$_3$)]$^-$

PhPd(OAc)(PPh$_3$)$_2$ $\xleftarrow{\text{PhI}}$ [Pd(OAc)(PPh$_3$)$_2$]$^-$ ⇌ [Pd(OAc)(PPh$_3$)$_3$]$^-$ $\downarrow$ 2PPh$_3$, −PPh$_3$
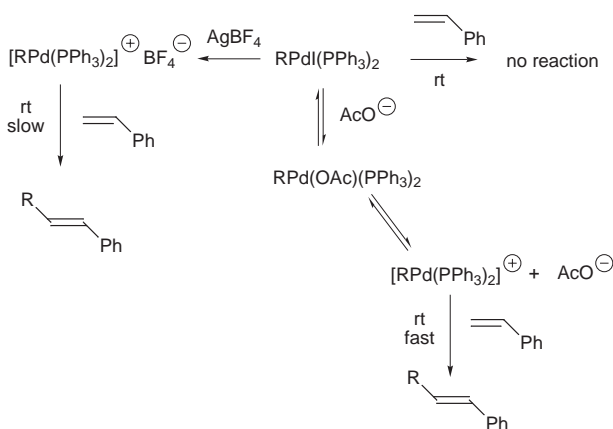
Scheme 3

Electrochemical studies indicate that anionic palladium complexes are more readily oxidised than the corresponding neutrals but that the rate of oxidative addition of iodobenzene is the same for both. Pentacoordinate anionic Pd(II) species have been proposed following the oxidative addition of aryl halides to [PdX(PPh$_3$)$_2$]$^-$ (Scheme 4).[8] The addition of excess acetate

[PdL$_2$Cl]$^\ominus$ + PhI ⟶ [Ph—Pd(L)(L)(I)Cl]$^\ominus$ $\xrightarrow{\text{S}}$ [Ph—Pd(L)(L)(I)S]$^\ominus$

S = solvent

↓

Ph—Pd(L)(L)—I

Scheme 4

anion (AcO$^-$) to PhPdI(PPh$_3$)$_2$ also results in an equilibrium with formation of PhPd(PPh$_3$)$_2$(OAc), probably *via* a dissociative mechanism involving iodide displacement. The affinity of Pd(II) for the anion X has been found to be Cl$^-$ > Br$^-$ > I$^-$ > AcO$^-$.[7] Since many of the catalyst precursors for Heck reactions involve adding 4 or more equivalents of L to assist in the stabilisation of the Pd(0), it is of interest to note that the addition of excess L (over the 3 equivalents required to generate [Pd(PPh$_3$)$_2$(OAc)]$^-$) retards the rate of oxidative addition of RX. These results would suggest that anionic complexes should favour the oxidative addition of RX to Pd(0).

The carbon–carbon bond forming step of the Heck reaction was studied using styrene which reacted with PhPd(PPh$_3$)$_2$(OAc) at room temperature in DMF to afford stilbene, whereas PhPdI(PPh$_3$)$_2$ did not react under these same conditions (Scheme 5).[7] When acetate anion was added to a

[RPd(PPh$_3$)$_2$]$^\oplus$ BF$_4$$^\ominus$ $\xleftarrow{\text{AgBF}_4}$ RPdI(PPh$_3$)$_2$ $\xrightarrow[\text{rt}]{\text{=Ph}}$ no reaction

rt slow ↓ =Ph ‖ AcO$^\ominus$

RPd(OAc)(PPh$_3$)$_2$

‖

[RPd(PPh$_3$)$_2$]$^\oplus$ + AcO$^\ominus$

rt fast ↓ =Ph

R—Ph (product)

Scheme 5

mixture of PhPdI(PPh$_3$)$_2$ and styrene the formation of stilbene was observed at room temperature. These observations are consistent with the dissociation of AcO$^-$ from PhPd(PPh$_3$)$_2$(OAc) to form an equilibrium mixture containing the cationic complex [PhPd(PPh$_3$)$_2$]$^+$. In contrast, the preformed cationic complex [PhPd(PPh$_3$)$_2$]$^+$ BF$_4$$^-$ reacted only slowly

with styrene at room temperature to afford stilbene. What can we infer from these observations? The counteranion would appear to play a crucial role in the electrophilicity of the Pd(II) species and it is likely that the formation of tight ion pairs with the palladium retards the coordination and insertion of the alkene.

These results do confirm that PdL₂ is not a major player in the oxidative addition process when anionic ligands such as halide or acetate are present. These stoichiometric studies have all been performed on the very reactive electrophile iodobenzene and the electron deficient alkene styrene. Aryl bromides are much less reactive than aryl iodides towards oxidative addition and require higher temperatures for the Heck reaction. When the catalyst system Pd(OAc)₂–PPh₃ is used in high temperature Heck reactions (usually above 100 °C) then the phenyl group is cleaved from the phosphine ligand at the arylpalladium(II) stage.[9] This causes the palladium catalyst to decompose prematurely and the phenyl group to be coupled to the alkene resulting in product contamination. Even under rather mild conditions, such as 60 °C in chloroform, preformed ArPd(PPh₃)₂Cl complexes have been reported to undergo aryl exchange and thus product contamination is a significant obstacle to the use of PPh₃ with less reactive electrophiles.[10] These high temperature conditions are necessary for aryl bromides containing electron donating groups and for un-reactive aryl chlorides because of the slow rate of oxidative addition at temperatures below 100 °C and so the necessity for more stable catalysts prompted investigations of alternative ligands.

3.2 Pd(OAc)₂ and P(o-tolyl)₃

In order to prolong the life of the palladium complex it has long been known that P(o-tolyl)₃ could be used, the assumption being that the bulky phosphine formed a stable PdL₂ species and that quaternisation of the phosphorus by the aryl halide (a problem because of the high temperatures) could be minimised. Recent studies of the reaction of Pd(OAc)₂ and P(o-tolyl)₃ have lead to a significant modification to the mechanism proposed in standard textbooks. The addition of slightly more than 1 equivalent of P(o-tolyl)₃ to Pd(OAc)₂ results in the formation of the dimeric palladacycle **3**, which in solution is in equilibrium with solvent bound monomers such as **4** (Scheme 6).[11] These palladacycles are extremely thermally stable showing no decomposition up to 250 °C. What is intriguing about these complexes is that they are Pd(II) species and do not appear to undergo an obvious reduction to Pd(0) during the Heck reaction. A Pd(II) to Pd(IV) sequence cannot be ruled out at this stage nor can the existence of a short lived, highly reactive Pd(0). Palladium(IV) species have been isolated and shown to be involved in the oxidative addition of particularly reactive alkyl halides (such as CH₃I) to Pd(II) complexes containing nitrogen chelating ligands and alkyl or aryl groups (**7** and **8**).[12] The Pd(II) to Pd(IV) sequence is normally only invoked when a Pd(0) to Pd(II) conversion is clearly not available or when the Pd(II) species cannot readily undergo β-hydride elimination or reductive elimination.[12]

For the Heck reaction involving monomer **4** palladacycles no oxidative addition of the aryl halide occurs in the absence of the alkene and then only at elevated temperatures. Catalysts such as **4** are capable of very high turnovers (>100 000 at 0.001% catalyst) for the coupling of butyl acrylate with 4-bromoaceto-phenone and in the presence of n-Bu₄NBr turnover numbers approaching 1 000 000 are possible.[11] Excess halide replaces the acetate group of **3** or **4** and forms **5** in the reaction mixture with the bridging halide **6** being isolated at the completion of the coupling. These catalysts, which appear to only operate at high temperatures, suggest that a number of alternative pathways are available for the Heck coupling and that a detailed unified mechanism is probably not operating under all conditions. A general mechanistic description of oxidative addition, alkene insertion and β-hydride elimination will then be the common

features for all Heck couplings with the oxidation state and charge on the palladium being dependent on the exact reaction conditions and ligands.

What are the advantages of using these heavy duty catalysts? Clearly they can be used for substrates which are reluctant to couple at room temperature because of a high activation energy for the oxidative addition, such as electron rich aryl bromides or aryl chlorides. The catalysts, or halide derivatives such as **6**, can be isolated from the reaction mixtures and recycled with little
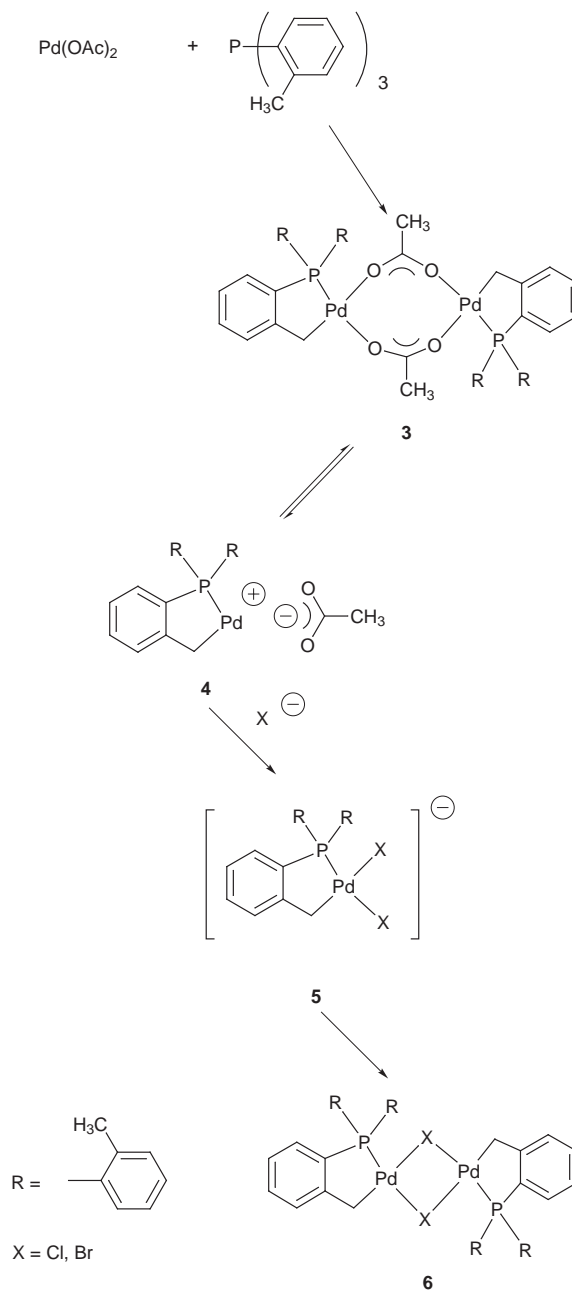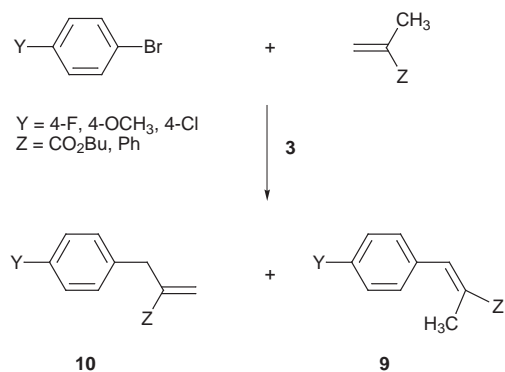
Scheme 6
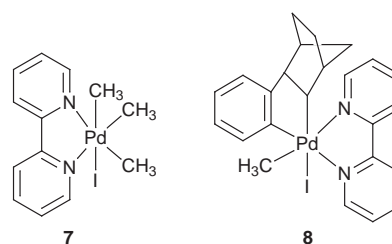
loss in activity. Only one equivalent of phosphine is required to generate the catalyst so that the retarding effect of excess phosphine seen in many studies can be avoided. These catalysts will have applications in industrial based processes and for thermally stable substrates.

Catalyst **3** can induce a coupling between 1,1-disubstituted alkenes and aryl bromides in the presence of amine bases to give the internal alkene **9** selectively, whereas in the presence of bases such as NaOAc and Na$_2$CO$_3$ a mixture of regioisomers (**9** and **10**) will be formed with the terminal alkene (**10**) as the major product (Scheme 7).[13] Interestingly, these authors have

Y = 4-F, 4-OCH$_3$, 4-Cl
Z = CO$_2$Bu, Ph

Scheme 7

proposed a reduction step whereby the palladacycle **3** is reduced to an unknown Pd(0) species and the rest of the coupling follows a traditional Heck mechanism (as in Scheme 1).

The search for alternative ligands which would not be cleaved at high temperatures prompted the development of N-heterocyclic carbenes as ligands.[14] The Pd(II) catalyst precursor **11** represents an example of non-chelating *cis* ligands with an X-ray crystal structure of **11** confirming the *cis* stereochemistry and the fact that the carbene ligands are rotated out of the plane (about 70°) formed by the palladium and associated iodide ligands. Carbene ligands will be good σ- and π-donors but poor π-acceptors in contrast to phosphines which are good σ-donors and good π-acceptors. These Pd(II) complexes show an initial induction period (presumably a reduction step) which can be eliminated by the addition of a reducing agent (such as hydrazine or formate). A particularly active catalyst which shows no induction period is formed from Pd(dba)$_2$ and 2 equivalents of 1,3-dimethyldihydroimidazol-2-ylidene. These carbene-containing catalysts are not active below 80 °C and so are most appropriate for non activated aryl bromides and aryl chlorides or substrates which are thermally stable.[14]

11　　　　　　　**12**
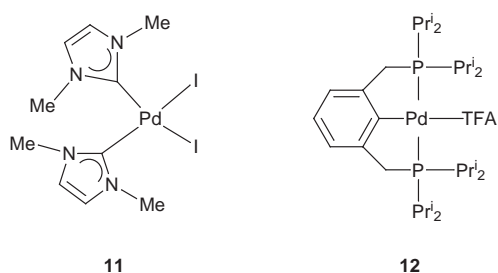
An alternative cyclometallated complex also displaying extraordinary stability at high temperature is derived from **12**.[15] This catalyst is not sensitive to air or moisture and Heck reactions can be conducted in air with no noticeable decomposition and the catalyst can even be recovered unchanged (apart from the trifluoroacetate, TFA, being replaced with the halide from RX) after 300 h at 140 °C. Since a cyclometallated palladium catalyst can be recovered from the reaction mixture it seems unlikely that Pd(0) intermediates are involved and a cycle

involving Pd(II) to Pd(IV) interconversions appears to be more likely.

Although the precise identities for the proposed Pd(II) and Pd(IV) intermediates have not been experimentally established, a mechanistic rationale involving them has been proposed by Shaw.[16] Since electron rich Pd(II) intermediates would be necessary in order to encourage oxidative addition, the conversion of a coordinated alkene into a σ-bonded alkyl species would increase the electron density around the Pd(II) and also explain the observation that catalysts such as **3** are inactive in the absence of alkene.[16] Alkenes are more susceptible to nucleophilic attack when coordinated to a Pd(II) complex and there are a number of nucleophiles (Y = AcO$^-$, X$^-$, HO$^-$, RNH$_2$ or R$_2$NH, Scheme 8) available under the typical

Y = AcO$^-$, X$^-$, HO$^-$, RNH$_2$ or R$_2$NH
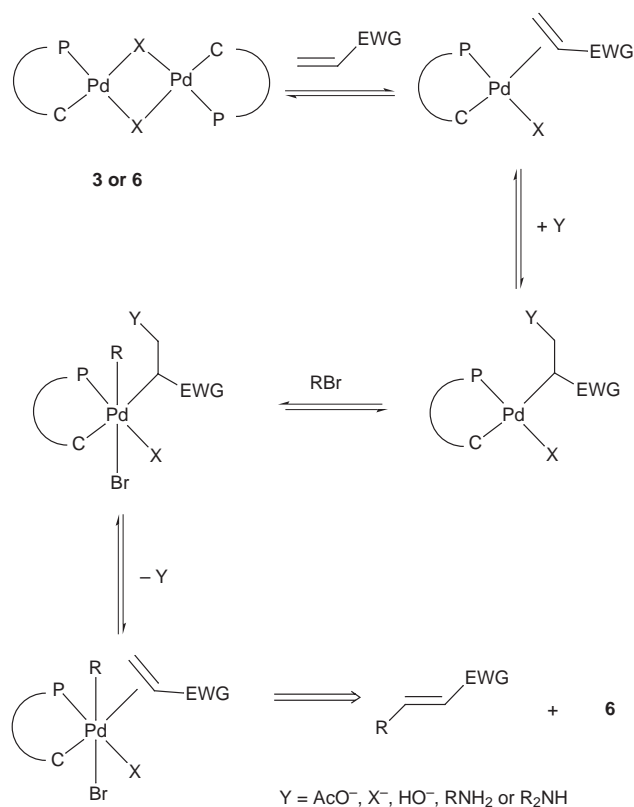
Scheme 8

conditions of a Heck reaction. Since catalysts involving Pd(II) to Pd(IV) interconversions operate at high temperatures, the addition of the nucleophile to the coordinated alkene is likely to be reversible. Shaw has also proposed that under the mild phase transfer conditions of Jeffery (discussed in detail below)[17] a reversible nucleophilic addition can also occur and so generate chelating dialkyl ligands which would facilitate oxidative addition to Pd(II).

3.3 Mild reaction conditions

3.3.1 PPh$_3$ ligands
Much of the recent effort directed towards the Heck reaction has centred on developing protocols which will allow coupling at temperatures below 60 °C with non activated alkenes. In order to achieve this the first requirement is a rapid oxidative addition of RX and the obvious choice would be an aryl or vinyl iodide which are known to oxidatively add to Pd(0) complexes at room temperature or below.[6] In the presence of halide anions, whether from the electrophile RX or from added *n*-Bu$_4$NX, anionic Pd(0) complexes are usually involved.[8] Such anionic species should be more nucleophilic than the corresponding neutral species and so react more rapidly with the electrophile RX.

An investigation of the reduction of PdCl₂L₂ catalyst (L = PPh₃) precursors has shown that in the presence of Cl⁻ the active Pd(0) species is [PdL₂Cl]⁻ (**13** in Scheme 9).[18] This
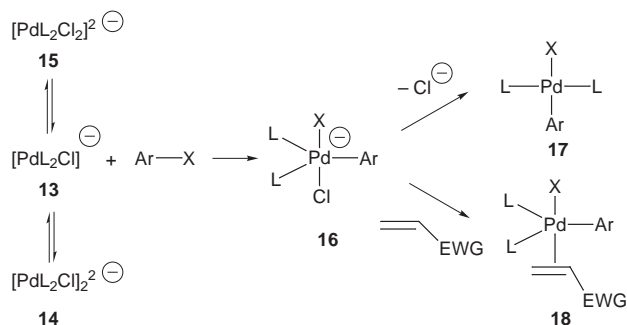
Scheme 9

anion is in equilibrium with the dimeric anion [PdL₂Cl]₂²⁻ (**14**) and, in the presence of excess Cl⁻, also with [PdL₂Cl₂]²⁻ (**15**). Aryl iodides (ArI) then undergo an oxidative addition to [PdL₂Cl]⁻ to generate a five coordinate anionic Pd(II) complex (**16**) which can eventually lead to ArPdL₂I (**17**) (the often proposed and sometimes observed product of stoichiometric reactions), this latter process being significantly accelerated by added Na⁺ ions which presumably form a tight Na⁺Cl⁻ ion pair and so assist in the removal of chloride ions. The formation of ArPdL₂I is not essential for the overall Heck cycle since an alkene can displace Cl⁻ from **16** and form **18**.[17]

An informative series of experiments was reported by Jeffery[17] on the use of phase transfer conditions for performing Heck reactions at 50–60 °C with Pd(OAc)₂ and PPh₃. In particular, the effects of added halide, PPh₃ and water showed that specific combinations of these additives can be beneficial for the coupling while other combinations can be highly detrimental depending on the particular base present. Using a standard Heck reaction involving reactive substrates, namely iodobenzene and methyl acrylate, Pd(OAc)₂ and 2 equivalents of PPh₃ at 60 °C, anhydrous conditions were found to be most effective when *n*-Bu₄NCl or *n*-Bu₄NHSO₄ was used in CH₃CN or DMF if either NaHCO₃ or KHCO₃ were the base. Anhydrous conditions were also necessary when using NaOAc, KOAc or *n*-Bu₄NOAc as the base, either with or without PPh₃, but in this case *n*-Bu₄NCl or *n*-Bu₄NBr were equally effective in promoting the coupling but *n*-Bu₄NHSO₄ was not. In stark contrast, the addition of water was clearly beneficial when the base was Na₂CO₃ or K₂CO₃. In fact, reactions could be performed in water, without any organic solvent, at room temperature provided both K₂CO₃ and *n*-Bu₄NX were present. Under these conditions the addition of PPh₃ was unnecessary. This dramatic accelerating effect of the base and added *n*-Bu₄NX depended on the presence of the tetraalkylammonium portion of the salt since addition of LiX or NaX had a negligible effect (probably because of the formation of tight ion pairs). For reactions performed in the absence of phosphine, *n*-Bu₄NCl was consistently an efficient promoter of the coupling, as was a combination of *n*-Bu₄NHSO₄ and KCl. Jeffery proposed that the accelerating effect of *n*-Bu₄NX resulted from an efficient base catalysed reduction of Pd(PPh₃)₂HX to regenerate the Pd(0) catalyst. It is also plausible that the added halide results in the formation of anionic Pd(0) complexes and five-coordinate Pd(II) intermediates which would also be expected to increase the rate of the oxidative addition and alkene insertion, respectively.[18] The accelerating effect of water was rationalised in terms of its influence on the concentration of halide or base in solution and in changing the solid–liquid phase (for organic solvents under anhydrous conditions) to liquid–liquid phase reaction conditions. Water has been reported to be a beneficial co-solvent for the Heck couplings of purine and pyrimidine iodides with 2,3-dihydrofuran with NaOAc or NaHCO₃ in combination with Et₃N.[19] These results highlight the complex

interactions which occur in the coordination sphere of the palladium during Heck reactions. It is clear that halides can have an accelerating affect on the Heck coupling and that reactions are possible under mild conditions (even room temperature) for suitably activated substrates.

So far we have discussed the oxidative addition of aryl or vinyl halides to Pd(0). Many of the recent examples of Heck reactions have involved the use of aryl or vinyl triflates (trifluoromethanesulfonates, OTf). The major difference with this substrate is the greater lability of the Pd–OTf bond compared to the Pd–X bond (X = Br, I) and its propensity to be readily displaced by other ligands, including solvents. Oxidative addition of Ar–OTf to Pd(PPh₃)₄ occurs readily at room temperature.[20] Electron withdrawing groups on the Ar–OTf substrate increase the rate of oxidative addition, consistent with a nucleophilic attack of the palladium on the electrophilic triflate. In the absence of added halide, it is assumed that Pd(PPh₃)₂ reacts with Ar–OTf to give cationic palladium(II) species.

In polar solvents separated ion pairs are formed (**19**) while in non polar solvents tight ion pairs are formed, whereas in the presence of added *n*-Bu₄NCl the square planar chloride complex **20** is formed (Scheme 10). The rate of oxidative
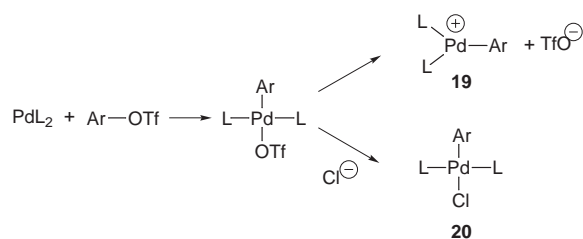
Scheme 10

addition of aryl triflates to Pd(0) increases in the presence of chloride ions (probably by formation of [PdL₂Cl]⁻ as described previously). The order of the oxidative addition of aryl electrophiles RX to Pd(0) is I > OTf ~ Br >> Cl.[20]

3.3.2 Solvent ligands
The combination of a vinyl triflate with phosphine and halide free phase transfer conditions proved to be an efficient procedure for the Heck couplings of non activated alkenes under mild conditions (50 °C) as depicted in Scheme 11.[21]
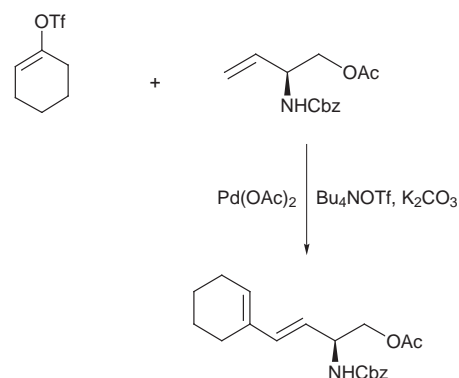
Scheme 11

Water was found to be necessary only when *n*-BuN₄Cl was used and made no difference to the yield or rate of reaction when *n*-Bu₄NOTf was used as the additive. In addition, only a catalytic quantity of *n*-Bu₄NOTf was required for an efficient coupling. Although water may induce a change from the solid–liquid phase to a liquid–liquid phase with a more rapid regeneration of the Pd(0) catalyst as proposed by Jeffery,[17] water could also accelerate the reaction rate by the formation of hydroxide anions which could act as a ligand for the palladium

(**21**, Scheme 12). In the absence of water but in the presence of Cl⁻ the catalytically active palladium species is ligated to chloride ions, whereas in water, chloride ligands could be displaced by hydroxide ions giving a weaker and kinetically more labile ligand and a faster Heck coupling. Halide ions appear to inhibit the Heck coupling of vinyl halides with alkenes lacking an activating electron withdrawing substituent, whereas the coupling of acrylates proceed satisfactorily in the presence of halide ions.

The coordination of a chloride ion to a Pd(II) complex inhibits the alkene insertion of an electron-rich alkene because of the repulsive interactions between the filled molecular orbital of the alkene and the filled 5s-orbital of the neutral Pd(II) complex.[22] The higher reactivity observed when using vinyl triflates and tetrabutylammonium triflate is then attributed to the high rate of dissociation of the triflate anion from the neutral Pd(II) intermediate and formation of a very reactive cationic palladium species (**22**).

3.3.3 Chelating phosphine ligands

Chelating phosphines are considered to be inappropriate for the Heck coupling of aryl halides with alkenes containing an electron withdrawing group but this situation is reversed for the couplings of electron rich alkenes with aryl and vinyl triflates [eqn. (2)].[6]

$$(2)$$
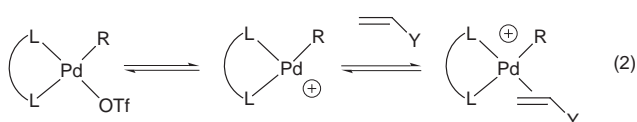
The key to the success of triflate electrophiles in Heck couplings rests with the formation of cationic Pd(II) intermediates which will bind electron-rich alkenes (poor π-acceptors but good σ-donors) strongly. On the other hand, neutral Pd(II) complexes will bind electron deficient alkenes preferentially as these alkenes are better π-acceptors but poorer σ-donors. It is possible to switch from cationic to neutral Pd(II) manifolds by the addition of a soluble halide source to reactions involving aryl or vinyl triflates and to switch from neutral to cationic Pd(II) manifolds by the addition of a halide sequestering agent (such as Ag₂CO₃ or AgOTf) to reactions involving aryl or vinyl halides. The regioselectivity of the Heck reaction is now better rationalised with an understanding of both neutral and cationic Pd(II) pathways.[6] Under neutral conditions alkenes containing an electron donating group attached directly to the alkene carbon will give mixtures of regioisomers largely determined by

steric factors, the key carbon–carbon bond forming step occurring at the least hindered carbon (Fig. 1).[6] Intermediates which are cationic will favour carbon–carbon bond formation at the least electron-rich terminus of the alkene or the terminus which can stabilise a developing positive charge (Fig. 1).[6]

Much of the recent mechanistic work on the Heck reaction has been concerned with the intermolecular, asymmetric Heck arylations of 2,3-dihydrofurans. Numerous reports have consistently shown that the Heck coupling of phenyl triflate with 2,3-dihydrofuran in the presence of (R)-BINAP (Fig. 2) and Pd(OAc)₂ will give (R)-2-aryl-2,3-dihydrofuran (**23**) in > 95% enantiomeric excess (ee), whereas the use of aryl iodides under these conditions will give only racemic products (Scheme 13).[23] The enantiomeric purity of (R)-**23** can be enhanced by a kinetic resolution involving the selective elimination of (S)-**23** through formation of the minor isomeric product (S)-**24**.

Molecular models show that (R)-**23** is derived from the cationic intermediate **25** while (S)-**24** is derived from the cationic intermediate **26** (Scheme 14). These two diastereomers result from the 2,3-dihydrofuran presenting a different face for coordination to the palladium. The enantiomeric purity of (R)-**23** and the yield of (S)-**24** are both dependent on the strength of the base used to reduce the Pd(II) hydride, with the highly basic 1,8-bis(dimethylamino)naphthalene giving the highest ee for (R)-**23** and the highest proportion of (S)-**24**. The rationalisation for these observations is that **25** undergoes a rapid β-hydride elimination to give an hydrido alkene **27** which experiences severe steric interactions between the phenyl ring of the dihydrofuran and the phenyl rings of the (R)-BINAP ligand. This unfavourable steric interaction can be alleviated by a rotation of the dihydrofuran ring to give **29** which can now undergo a series of rapid β-hydride additions and eliminations to give (R)-**23**. For **26**, the initial hydrido alkene **28** will not experience these unfavourable steric interactions so that rotation of the dihydrofuran is less likely and **28** can form (S)-**24** directly (Scheme 14). These studies have highlighted the ease with which reversible β-hydride additions and eliminations will take place during Heck couplings.

In a mechanistic study of this reaction using (S)-BINAP extensive use of ³¹P NMR spectroscopy has revealed the ease with which alkene insertions can take place and the importance of the base in minimising the lifetime of the hydrido Pd(II) intermediates.[24] Isomer (S)-**23** was formed in up to 91% enantiomeric excess along with the minor isomeric product (R)-**24**,[24] consistent with previous reports based on (R)-BINAP.[23] Intermediate **30** was characterised by ³¹P and two dimensional ¹H NMR spectroscopy as well as mass spectrometry (Scheme 15). Carbon–carbon bond formation occurred at −30 °C and **30** was stable at this temperature for

X = AcO⁻, Cl⁻, HO⁻, TfO⁻   L = solvent
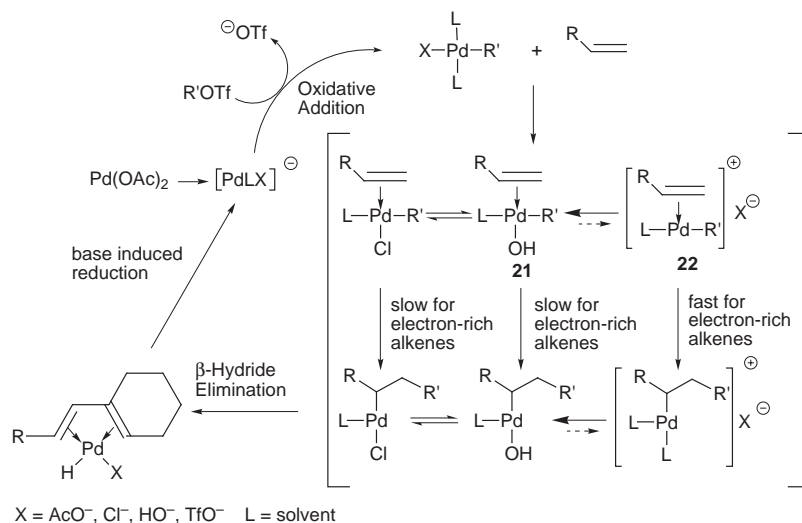
Scheme 12

several hours.[24] In the absence of base the palladium hydride adds to the 2,3-dihydrofuran to give a mixture of diastereomers **31**, whereas in the presence of a strong organic base none of this product was observed.

The ability of the chelating phosphine to maintain the bidentate coordination is essential to the proposed rationalisation of the enantioselectivity of these Heck reactions.

The use of chiral phosphinooxazoline ligands (such as the *tert*-butyloxazoline in Fig. 2) has further enhanced the ee's
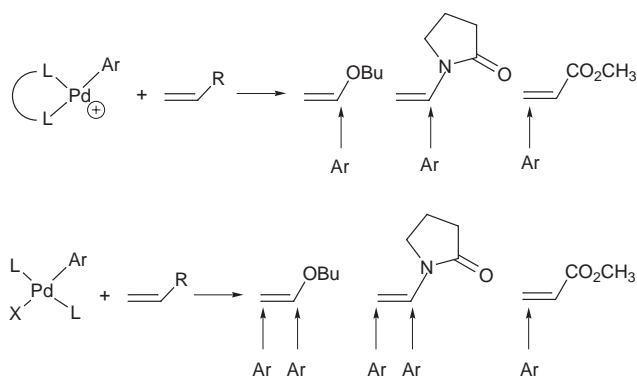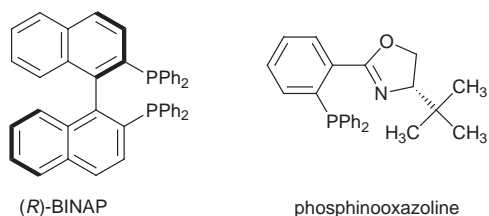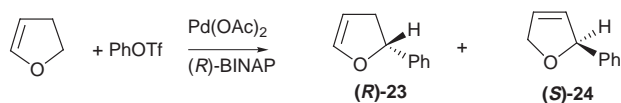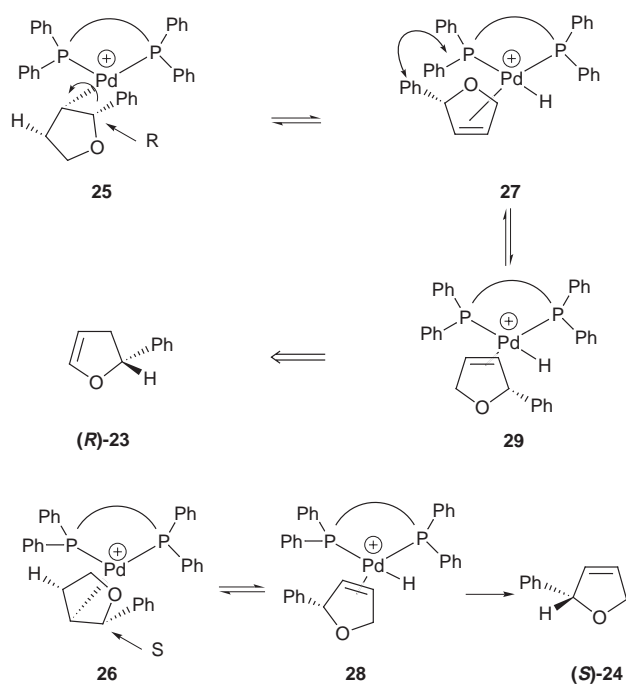

Fig. 1

(*R*)-BINAP   phosphinooxazoline
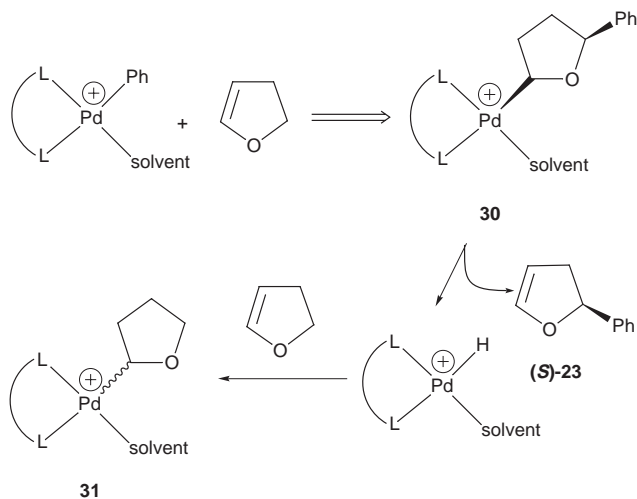
Fig. 2
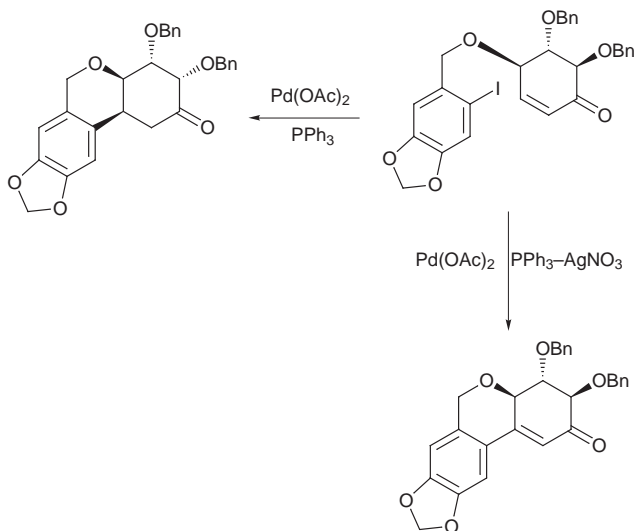

Scheme 13

Scheme 14

Scheme 15

available from these reactions and offers an alternative product profile compared to BINAP.[25] The major product from the reaction of phenyl triflate with 2,3-dihydrofuran in the presence of (*R*)-BINAP was (*R*)-**23** with (*S*)-**24** being a minor yet persistent byproduct.[23] The same reaction performed with (*S*)-phosphinooxazoline (Fig. 2) gave (*R*)-**24** as the sole product (97% ee) and none of the isomeric 2,3-dihydrofuran **23**, therefore suggesting that reversible β-hydride elimination and addition is less favourable with this ligand. The catalysts formed from phosphinooxazoline ligands are less reactive than those formed from BINAP with Heck couplings typically performed at 50–80 °C over 3–7 days. The reactivity profile for this ligand suggested that cationic Pd(II) intermediates were involved, as did the observation that chloride ions dramatically reduced the rate of coupling. 2,3-Dihydropyrrole can also be used successfully for asymmetric Heck couplings as can nonactivated alkenes such as cyclopentene and cyclohexene (although with lower ee's).

3.3.4 Intramolecular Heck couplings
The early reports of asymmetric Heck reactions concentrated on intramolecular examples which involved the formation of tertiary centres, usually used (*R*)-BINAP as the chiral ligand and were performed in polar, aprotic solvents such as *N*-methylpyrrolidin-2-one.[3,5] When aryl or vinyl halides were used as the electrophile, a halide sequestering agent (Ag⁺) was added to ensure a cationic Pd(II) intermediate. The use of AgOAc was found to be detrimental to high ee's since AcO⁻ would bind strongly to the Pd(II) and discourage formation of the necessary cation. The most efficacious sequestering agent was Ag₃PO₄ which afforded high ee's because of the low nucleophilicity of PO₄³⁻ and consequential low affinity for Pd(II). If triflates were used instead of halides then a Ag⁺ source was unnecessary and nonpolar solvents preferred.

The selectivity of Ag⁺ salts in effecting a non-reductive cyclisation was elegantly demonstrated during the synthesis of Pancratistatin as outlined in Scheme 16.[26] In the absence of Ag⁺ salts only the reductive cyclisation product was observed (the inversion of the OBn alpha to the carbonyl was inconsequential to the Heck coupling).

The inherent reluctance of tri- and tetrasubstituted alkenes to participate in Heck couplings can be overcome by using an intramolecular reaction rather than a bimolecular one.[4] The success of this approach has been demonstrated with the construction of sterically hindered quaternary centres.[4] During an intermolecular Heck coupling the alkene can present two alternative faces to the palladium with steric hindrance between the substituents on the alkene and the ligands on the palladium determining which face is preferred. For an intramolecular
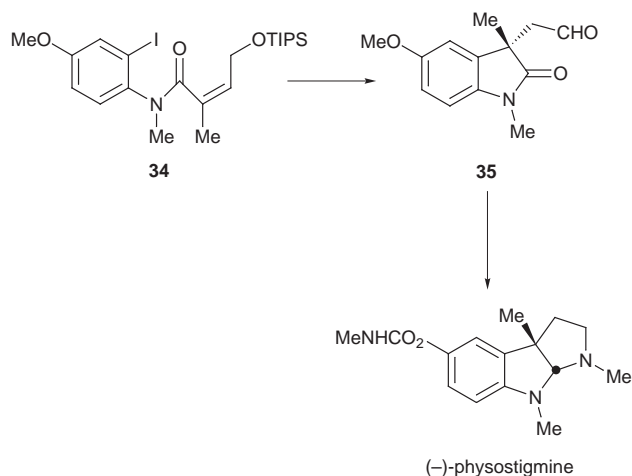
Scheme 16

Heck coupling restrictions in the conformation of the backbone linking the alkene to the electrophilic centre will usually determine a preferred orientation of the alkene. During the total synthesis of *Amaryllidaceae* alkaloids the stereochemistry of the intramolecular Heck coupling was shown to favour an eclipsed orientation of the Pd–C bond and the alkene (Scheme 17).[4] Using the catalytic system Pd(OAc)$_2$–PPh$_3$–Ag$_2$CO$_3$ in THF at 66 °C a single cyclised product, **32**, was formed in 90% yield. The epimeric product **33** was not detected, suggesting that the preferred orientation of the tethered alkene is eclipsed (assuming the conformations shown in Scheme 17).
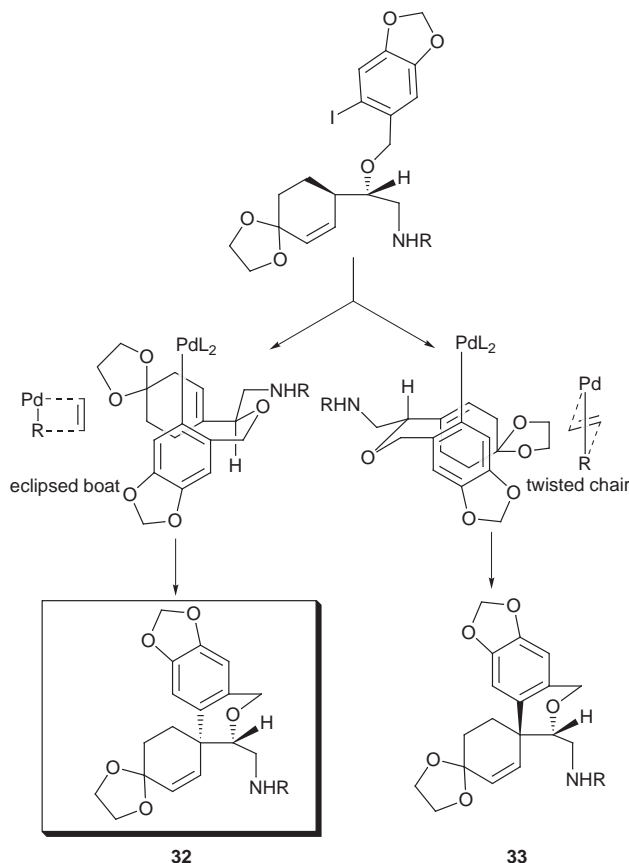
Scheme 17

It is also possible to form quaternary carbon centres with high enantioselectivity by an intramolecular Heck coupling using either (*R*)- or (*S*)-BINAP and Pd$_2$dba$_3$**·**CHCl$_3$.[4] Using (*S*)-BINAP and *Z* alkene **34** an intramolecular Heck coupling

will form 3,3-disubstituted-2-oxindole **35** in 95% ee and eventually (−)-physostigmine, whereas **34** and (*R*)-BINAP can be used to form *ent*-(+)-physostigmine (Scheme 18). Analogues of **34** with an *E* stereochemistry around the alkene also cyclised but with much lower ee's (50%). The interesting feature of these intramolecular Heck transformations is the high ee's observed even in the presence of halide. Earlier discussions in this review have highlighted the fact that halide free conditions were necessary to effect high ee's in intermolecular couplings.
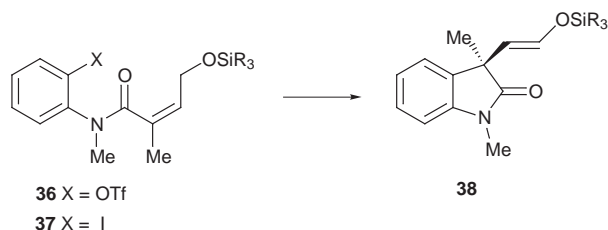
Scheme 18

These cyclisations result from an equatorial orientation of the large group and an eclipsed conformation of the Pd–C σ-bond and the alkene. For the formation of large rings *via* an intramolecular Heck coupling an *endo* selectivity is usually observed because both faces of the alkene are accessible [eqn. 3].[3] For medium sized rings a mixture of *endo* and *exo* cyclisation is often observed [eqn. (4)] while for small rings *exo* cyclisation is predominant [eqn. (5)]. It is noted that it is possible to design substrates which cyclise contrary to these general observations.[3]
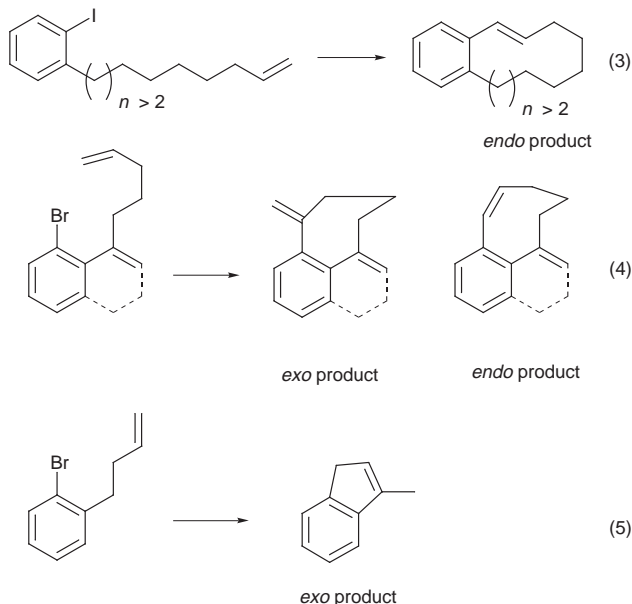
A further example of this difference in the reaction pathways for inter- and intramolecular Heck reactions is seen in the greatly enhanced enantioselectivity resulting from the addition of *n*-Bu$_4$NX to Pd–(*R*)-BINAP induced cyclisation of triflate **36** (ee of 90–95%, Scheme 19).[27] In the absence of *n*-Bu$_4$NX an ee of 43% was observed. For the cyclisation of iodide **37** using this same catalyst an ee of 91–95% was observed in the presence or absence of added halide, yet the ee dropped dramatically to 43%
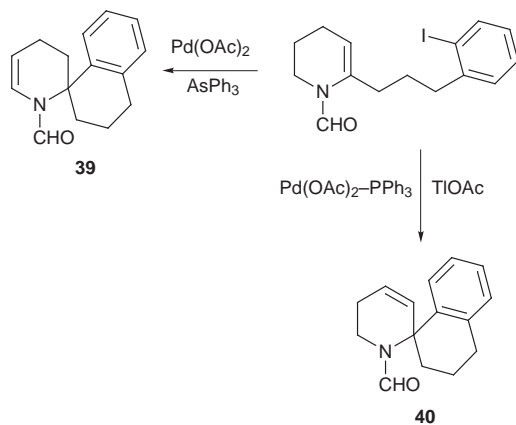
Scheme 19

for the iodide in the presence of AgOTf. In order to rationalise these observations a five-coordinate neutral Pd(II) precursor to a cationic Pd(II) intermediate was proposed and the effect of the added halide was to divert the palladium from a dissociative pathway involving triflate loss (Scheme 20).
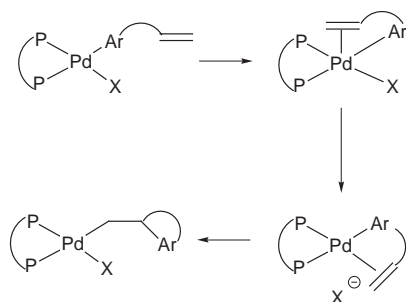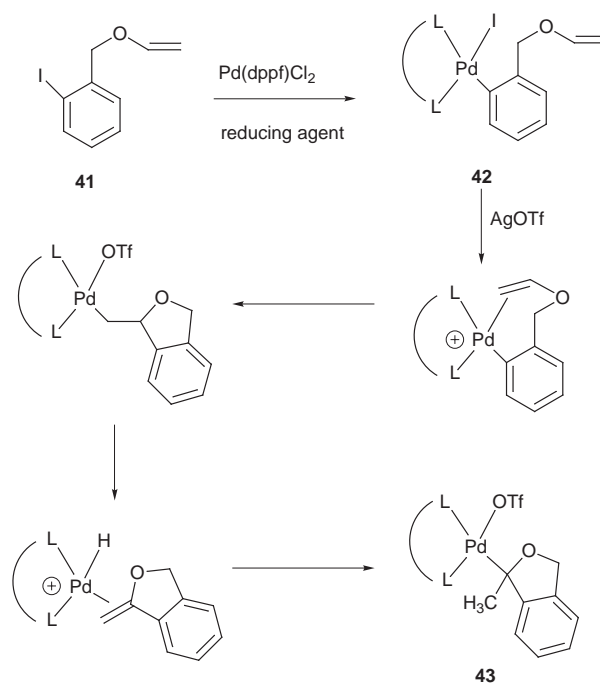

Scheme 20

By using the poorly coordinating ligand AsPh$_3$ in conjunction with Pd(OAc)$_2$ it is possible to encourage reversible β-hydride eliminations and additions and so form the thermodynamically more stable alkene (**39**) by an intramolecular cyclisation (Scheme 21).[28] Alternatively, by using a halide sequestering agent such as TlOAc and PPh$_3$ the expected spiro tetra-hydropyridine **40** can be formed with minimum double bond isomerisation.

Scheme 21

A stoichiometric investigation of the intermediates formed during the intramolecular Heck cyclisation of **41** with Pd(dppf) (dppf = diphenylphosphinoferrocene) resulted in the isolation of **42** (Scheme 22).[29] The X-ray structure of **42** showed a distorted square planar structure with the aryl group perpendicular to the mean square plane of the palladium and associated ligands and no interaction of the tethered alkene with the metal centre. Complex **42** was stable at room temperature showing no signs of undergoing the Heck cyclisation. Reaction of **42** with AgOTf at −78 °C caused an immediate precipitation of AgI and the only species detected by NMR at −40 °C was **43**, the product of insertion and reversible β-hydride elimination and addition.[29] This implies that the insertion of the palladium–aryl
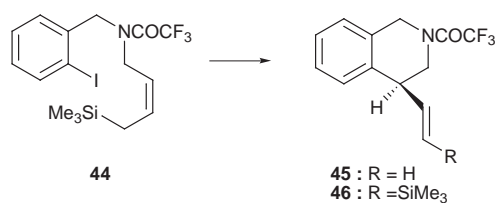

Scheme 22

bond into the alkene is rapid and that the β-hydride elimination and addition is also rapid at this low temperature. This sequence implies that if the stereochemistry of the intermediates is favourable then rapid Heck coupling can take place at low temperatures.

4 Recent modifications to traditional reaction conditions

An effective method for controlling the position of the double bond from an asymmetric intramolecular Heck coupling is the use of a terminal trimethylsilyl group as in **44**.[30] A catalyst system consisting of Pd(OAc)$_2$, PPh$_3$, KOAc and n-Pr$_4$NBr gave the vinyl product **45**, whereas the catalyst system Pd$_2$dba$_3$–PPh$_3$–Ag$_2$O gave predominantly the vinyl silane **46**, indicating that the presence of the silane has completely suppressed alkene isomerisation (Scheme 23).

45 : R = H
46 : R = SiMe$_3$

Scheme 23

With the increased interest in using Heck reactions for industrial processes and for the synthesis of pharmaceuticals the loss of palladium catalyst and product contamination with the catalyst have emerged as serious issues. The use of controlled-pore glass beads coated with a palladium catalyst derived from Pd(OAc)$_2$ or PdCl$_2$ and a water soluble phosphine ligand (m-NaO$_3$SC$_6$H$_4$)$_3$P has been shown to catalyse the classical Heck reaction between aryl bromides or iodides and acrylates with less than 1 ppm leaching of the palladium.[31] A silica-supported poly-γ-mercaptopropylsiloxane Pd(0) catalyst, prepared from the condensation of fused silica and γ-mercaptopropyltriethoxysilane and PdCl$_2$ followed by reduction with hydrazine, can be used to prepare functionalised styrenes and acrylic acids in good yield.[32] The catalyst can be recovered by simple filtration and reused with only a 3% reduction in activity for the second cycle. Only 0.4% catalyst need be employed for the couplings and the reduced catalyst can

be exposed to air for up to a week with no apparent reduction in activity. The disadvantage for this particular catalyst is that only aryl iodides and not aryl bromides will couple with the acrylates.

5 Summary of protocols

Can we now propose a series of protocols which can be used to assist the practising chemist in performing a successful Heck coupling? There are no certainties in synthesis yet the large body of published data and detailed mechanistic information can be used to establish some general guidelines. For *intermolecular* couplings involving reactive electrophiles (aryl or vinyl iodides) and alkenes containing an electron withdrawing group a traditional catalyst systems such as Pd(OAc)$_2$ and 2–4 equivalents of L or PdL$_2$Cl$_2$ or PdL$_4$ [L = PPh$_3$ or P(*o*-tolyl)$_3$] with an organic or inorganic base will usually suffice. Such systems will usually require temperatures in the range 50–100 °C. In order to lower the temperature the most effective protocol is to add R$_4$NX (X = Cl, Br) and use an aqueous solvent with K$_2$CO$_3$ as the base. For electrophiles which undergo oxidative addition more slowly (aryl bromides with electron donating groups or aryl chlorides) high temperatures (above 120 °C) are usually required and a ligand which will not decompose is essential for a long lived catalyst (L = PPh$_3$ will not be suitable). For aryl or vinyl triflates with alkenes containing an electron withdrawing group a traditional catalyst system can also be used. For alkenes which do not contain an electron withdrawing group then halide free conditions, achieved by either using aryl or vinyl triflates as the electrophile or adding a halide sequestering agent (Ag$^+$) for aryl or vinyl halides, will be advantageous. For *intramolecular* Heck cyclisations the reaction conditions appear to vary depending on whether a tertiary or quaternary centre is being formed, on the ring size and the stereochemistry of the alkene. The presence of halides does not appear to impede the cyclisation at elevated temperatures and can be beneficial for high ee's in asymmetric Heck couplings. The use of halide free conditions can produce rapid Heck couplings but variable ee's for asymmetric cyclisations.

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