Pergamon

Tetrahedron 57 (2001) 7449–7476

TETRAHEDRON

Tetrahedron report number 582

Advances in the Heck chemistry of aryl bromides and chlorides

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Received 25 June 2001

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1. Introduction

The palladium-catalysed arylation of an alkene with an organic halide (Scheme 1) was first reported by Mizoroki[1] and Heck[2] in the early 1970s. The classical reaction involves bond formation between two sp^2 carbon centres by an overall substitution of a C–H bond of an alkene by

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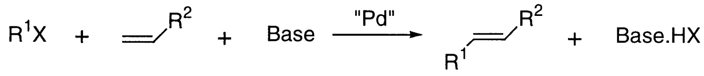
PII: S0040-4020(01)00665-2



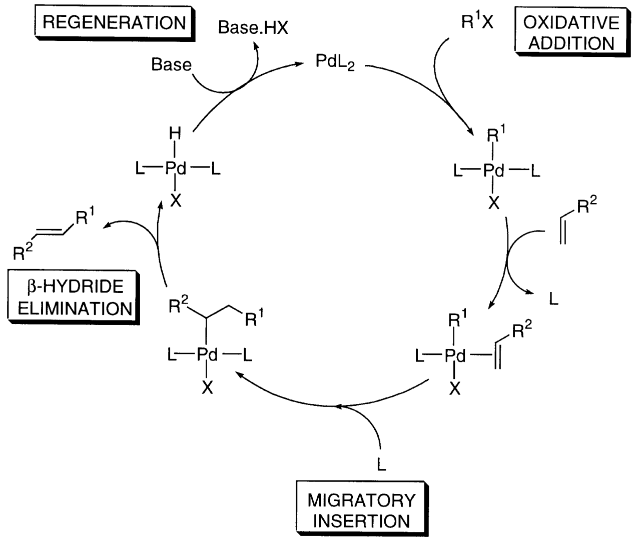
Scheme 1.

R^1 from the R^1X substrate (where R^1=aryl or vinyl; X=I or Br; R^2=electron withdrawing or releasing group) under basic conditions. The transformation has since become known as the Heck reaction.

Since its discovery, the methodology has been found to be highly versatile and applicable to a wide range of aryl species Ar–X, where X=Cl, Br, I, OTf, OTs and N_2^+. A diverse range of olefins has also been found to undergo the Heck reaction readily.

The Heck reaction has been studied intensively and numerous excellent surveys on a wide variety of different aspects of this reaction have been published, including the initial reviews by Heck.[3] Interestingly, the reaction was scarcely used in the first two decades following its discovery. Its popularity only started to flourish in the mid-1980s when synthetic chemists found that they were able to control the selectivity by using certain reaction protocols to give fairly predictable results. This led to the publication of a handful of review articles from the mid-1990s onwards, on the development of ligands for the reaction,[4] as well as the application of the Heck reaction to natural product synthesis.[5] More recently, coverage has been provided on the reactivity and selectivity of the Heck reaction,[6] as well as the development of the subject in the light of mechanistic studies.[7]

This review aims to draw attention to future challenges in the area by highlighting advances concerning Heck coupling reactions using aryl bromides and chlorides. These halides are more reluctant to undergo catalytic reactions due to their stronger C–X bonds, a problem made worse if the aryl group carries electron-rich substituents. Aryl bromides and chlorides are however much more useful substrates to synthetic chemists, as they are cheaper and more readily available.



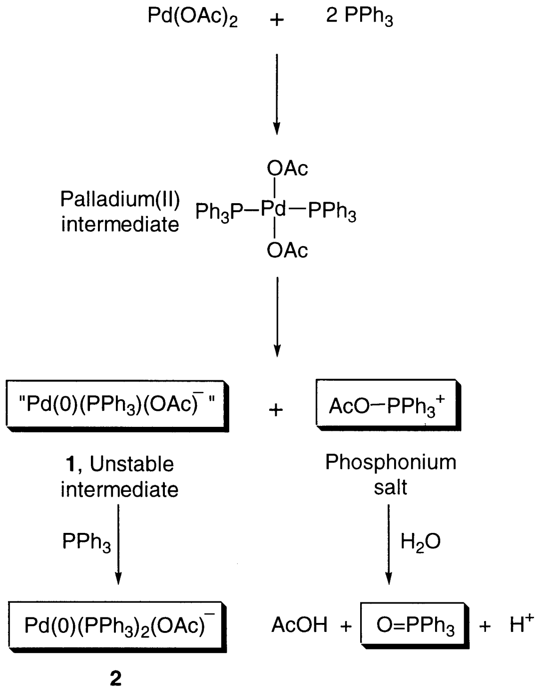
Scheme 2. Traditional mechanism of the Heck reaction. R^1=Ar or vinyl; R^2=preferentially an EWG; L=ligand; X=I, Br.

Surveying the current literature, there appears to be some confusion concerning the reactivity of aryl halides. In many studies, reactive aryl iodide substrates are routinely used to test the efficiency of a novel catalytic system, when it has been clearly demonstrated that unligated palladium precursors can easily achieve extremely high turnover numbers (TONs), i.e. in millions.[8] Furthermore, the couplings of aryl iodide and bromide with methyl acrylate have very different rate-determining steps.[8] This has important implications for the development of catalysts for the activation of aryl bromides and chlorides. Numerous papers report catalytic systems with impressive TONs. The majority of these studies were, however, performed using electron-poor aryl halides, typically 4-bromoacetophenone, and electron-poor olefins such as acrylates and styrenes.

The current challenge lies in the development of catalytic systems that will activate unreactive aryl halides towards Heck catalysis, especially aryl chlorides where the TONs still remain in the lower hundreds. Significant strides have been made within the last two years (1998–2000). Although certain aspects of this report have been covered by other authors in more general terms,[9] a review addressing the Heck reactions of aryl bromides and chlorides specifically is considered to be particularly timely. The purpose of this article is therefore to present the underlying principles and outcomes of the latest efforts to activate these more difficult substrates for Heck catalysis, thus highlighting the challenges in this highly competitive area.

1.1. Traditional mechanism

The mechanism for the Heck reaction has traditionally been presented as illustrated in Scheme 2. Palladium salts [e.g. $Pd(OAc)_2$, $PdCl_2$] alone can be used, although the addition of certain ligands (L) is often found to improve the efficiency of the reaction. The palladium catalytic precursor has been postulated as a coordinatively unsaturated 14-electron species (PdL_2). Oxidative addition of R^1X occurs to generate a *cis*-$RPdXL_2$ species, which consequently isomerises to the thermodynamically more stable *trans* configuration. In order for the alkene to insert into the complex, a free coordination site is necessary and creation of this has generally been accepted as involving the deligation of an uncharged ligand to give a neutral Pd complex to which the alkene coordinates. The C–C bond-forming step, where the alkene inserts into the Pd–R^1 bond, results in the formation of an unstable σ-bond. Rotation about the C–C bond and β-hydride elimination produces the new substituted alkene, which is then eliminated from the system. In order for the cycle to continue, regeneration of the active PdL_2 complex is effected by the addition of a base to remove HX from the inactive $HPdXL_2$ complex.



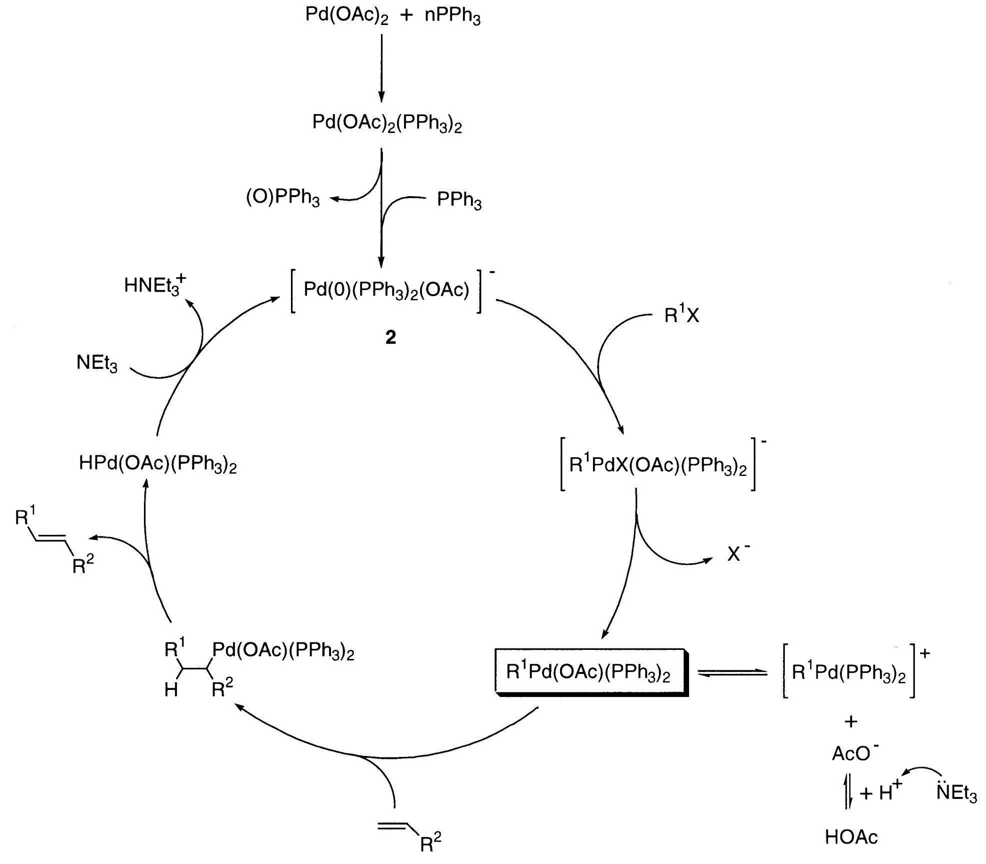
Scheme 3. Formation of the active catalytic species in the Heck cycle.

1.2. Mechanistic developments

There is an emerging body of work on investigating the mechanism of the Heck reaction, including theoretical studies on the more elusive alkene insertion step.[10,11] The task is monumental considering the myriad of reaction conditions, substrates and reagents that should be taken into account, and the sensitivity of the reaction to subtle changes in the reaction conditions. Most importantly, caution needs to be exercised whilst discerning the results of such studies: the majority are carried out on isolated species in the absence of additives, and therefore might not necessarily reflect the system under turnover conditions. Many investigations are also conducted at low temperatures, which could exclude the observation of high-energy intermediates involved in catalysis at conventional reaction temperatures (typically at about 140°C). Despite these limitations, these studies do still provide valuable insights into the inherent complexity of the problem.

Using electrochemical techniques, Amatore and Jutand have made several important contributions in this area towards the identification of effective catalytic precursors and intermediates.[12] They were the first group to reveal that the Heck mechanism based on [$Pd(OAc)_2$+n PPh_3] is far more complicated than was originally thought.[13]

The same workers proposed that the initial complex formed on mixing $Pd(OAc)_2$ with n equivalents of PPh_3 (where $n \geq 2$) is the unstable species $Pd(PPh_3)_2(OAc)_2$ (Scheme 3). A ligated PPh_3 causes the complex to undergo an intramolecular reduction, generating a short-lived palladium(0) species, **1**. Coordination of another molecule of PPh_3 results in the formation of $[Pd(0)(PPh_3)_2(OAc)]^-$, **2**, the active catalytic species that initiates the Heck cycle. The reducing



Scheme 4. Amatore and Jutand mechanism for a $Pd(OAc)_2$+n PPh_3 catalytic cycle.

PPh_3 forms a phosphonium salt and the adventitious presence of water results in the formation of acetic acid, triphenylphosphine oxide and protons.

The anionic species, $[Pd(0)(PPh_3)_2(OAc)]^-$, **2**, is therefore postulated as the active moiety that initiates the catalytic cycle (Scheme 4), which agrees with an earlier postulation by Spencer[14] of the possibility of acetate-containing palladium intermediates in the catalytic cycle of aryl chlorides. Oxidative addition of R^1X to the anionic complex proceeds rapidly to give a transitory anionic pentacoordinated complex. After loss of the halide ion X^-, the neutral *trans*-$R^1Pd(OAc)(PPh_3)_2$ species is found to be the key reactive intermediate. This result is very different from the traditional mechanism where the post-oxidative addition complex was proposed to be *trans*-R^1PdXL_2. Based on this, and other, findings, a new improved catalytic cycle was proposed for Heck reactions of iodobenzene. Different sets of intermediates may well operate for Heck reactions involving aryl bromides and chlorides, as the type of anion (X^-) involved plays an important role in defining the real structure and reactivity of the resulting reaction intermediates.[12,15,16] In addition, studies carried out with other palladium precursors, e.g. $Pd(dba)_2$ and $Pd(PPh_3)_4$, revealed that the catalytic activity and selectivity can no longer be adequately described through a unified, simple diagram. In each example, it is clear that the reaction intermediates and their associated reactivities are intimately associated with the chosen catalyst, substrates, additives and reaction conditions.[6] Discoveries of new catalytic systems over the last few years have resulted in several novel mechanistic hypotheses, which have been the subject of countless speculation and debates.

2. Limitations of the Heck reaction

2.1. C–X Bond strength

The oxidative addition of Ar–X to palladium(0) species has been the most well studied step of the Heck reaction as it is a common initiation stage for many palladium-catalysed reactions involving aryl halide substrates. The order of bond strengths for aryl halides is: Ar–Cl>Ar–Br>Ar–I, which corresponds to the experimentally found bond dissociation energies of 96, 81 and 65 kcal/mol, respectively.[17] This trend is also reflected in the ability of aryl halides to undergo oxidative addition with palladium(0) complexes: $ArCl<ArBr\ll ArI$. Electron-donating substituents on the aryl group also make the oxidative addition more difficult and, as a result, electron-poor aryl halides are often referred to as 'activated', and electron-rich aryl groups as 'deactivated'.

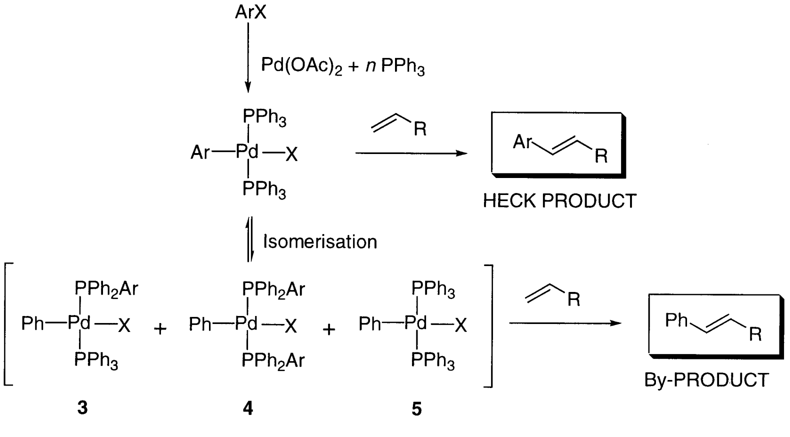
With these factors in mind, it is, perhaps, not surprising that the Heck reaction has evolved such that the conditions developed have mainly focussed on using aryl iodides as substrates. There are, however, a number of advantages in developing procedures to efficiently utilise aryl bromides and the synthetically more challenging aryl chlorides: (a) aryl iodides are often more expensive than either aryl bromides or chlorides and are less desirable in terms of atom economy; (b) aryl chlorides are more widely available; and (c) aryl chlorides are inherently more robust and can tolerate a wider range of reaction protocols. One of the biggest challenges for Heck chemistry is the development of an efficient system that can achieve high turnovers for deactivated aryl halides such as 4-chloroanisole.

2.2. P–C Bond cleavage and catalyst decomposition

Aryl bromides and chlorides are often unreactive towards oxidative addition under mild reaction conditions, and reaction will only occur, if at all, at much higher temperatures than the iodides. Triarylphosphine ligands have traditionally been used in the Heck reaction to promote the lifetime of the catalyst, temperatures above 120°C, however, often lead to competitive degradation of the palladium catalyst and the formation of unwanted by-products through thermally-activated P–C bond cleavage of a coordinated phosphine ligand.

P–C bond cleavage was first observed to occur at 60°C in $(Ph_3P)_2Pd(Ph)(I)$,[18] and was subsequently observed for both activated and deactivated aryl bromides and chlorides at higher temperatures (Scheme 5).[19–21]

Oxidative addition of ArX (X=Br and I) gives the *trans*-$ArPdX(PPh_3)_2$ intermediate which can react with $H_2C{=}CHR$ to form the expected Heck product. The complex may undergo P–C bond cleavage and aryl scrambling, however, to give the isomerised intermediate **3** (experimental evidence showed that a maximum of two



Scheme 5. Mechanism of by-product formation.

phenyl groups can be cleaved per phosphine ligand). Subsequent intermolecular phosphine scrambling of **3** accounts for the formation of **4** and **5**, and **3–5** can react with the olefin to furnish an undesired by-product.

The thermal stability of complexes of the type $[(Ph_3P)_2Pd(Ph)(X)]$ (where X=F, Cl, Br and I) has been studied in some detail, and aryl scrambling of the aryl iodide complex was found to be much more facile than that of the analogous bromide and chloride.[22] Conversely, the presence of electron-withdrawing groups on both the phosphine and the palladium-bound aryl groups was found to suppress aryl scrambling.[23]

Several mechanisms have been proposed for the P–C bond cleavage reaction in $[Pd(OAc)_2+PPh_3+\text{alkene}]$ systems, including a nucleophilic 1,2-migration of a phenyl group from the phosphine to the palladium atom,[24] and an oxidative addition of a P–Ph bond to a palladium(0) species.[25] An alternative route involves the reversible addition and elimination of quaternary phosphonium salts $Ar^1Ar^2{}_3P^+X^-$ from arylpalladium(II) complexes.[22,26]

P–C bond cleavage was also seen as a contributing factor to the decomposition of the catalytic species by creating unstable subcoordinated palladium complexes that eventually precipitated out of solution as palladium black.[22,27]

3. Advances in aryl bromide and chloride Heck chemistry

It is well documented that electron-poor 'activated' aryl halides undergo Heck reactions more easily than electron-rich substrates and this general trend has been observed for both aryl bromides and chlorides. Viewed simplistically, the role of the ligands is to stabilise the palladium species in the catalytic cycle, in order to prevent premature catalyst deactivation. A logical step in developing methods to activate aryl bromides and chlorides for Heck chemistry would be to modify the existing ligands or apply known compounds in a novel way. As Beletskaya and Cheprakov have succinctly described, however, it is impossible to accurately predict good ligands, and advances to date have largely been due to trial and error.[6] In the following sections, the efficacy of various ligands in promoting the reactivity of aryl bromides and chlorides towards the Heck arylation reaction is evaluated, along with associated mechanistic studies and rationale.

3.1. Phosphorus ligands

3.1.1. Monodentate phosphine ligands. A recent paper which examined the role of *para*-substituted triarylphosphines, $P(p\text{-X–}C_6H_4)_3$, on the rate of the Heck reaction between 4-bromoacetophenone and methyl acrylate revealed a linear Hammett relationship, where the more electron-rich arylphosphines induced the fastest and highest turnovers.[8] Among the 'traditional' triarylphosphine ligands, it was found that tri-*o*-tolylphosphine gives the best results for aryl bromides.[27] In the coupling of 4-bromophenol with methyl acrylate, the use of tri-*o*-tolylphosphine, $[P(o\text{-Tol})_3]$, produced *trans*-methyl-4′-hydroxycinnamate in 98% yield (Table 1; entry 1), whereas the use of triphenylphosphine (PPh_3) gave only 3% (entry 2). For bromobenzene, $P(o\text{-Tol})_3$ and PPh_3 proved to be essentially equal in activity and yields of 68 and 65% could be achieved with lower concentrations of the catalyst (entries 3 and 4).[14] On increasing the amount of catalyst to 2 mol%, conversions of 99 and 94% could be achieved (entries 5 and 6).[21] The overall yields of the reactions with activated aryl bromides were generally very similar, although the type of ligands utilised had an effect on the turnover rates (entries 7–9).[29] Additionally, with highly activated 1-bromo-4-nitrobenzene, TONs of 100 000 can be achieved (entry 10).

Efforts to apply the Heck reaction to aryl chlorides in the early 1980s met with little success. $P(o\text{-Tol})_3$ did not give good conversions for aryl chlorides as it had with the bromides.[14] For electron-poor aryl chlorides the phosphines of choice were PPh_3 or $P(p\text{-Tol})_3$, which gave comparable yields of ca. 69% (Table 2; entries 1 and 2), whereas a poor yield (33%) was obtained using the *ortho*-substituted phosphine, $P(o\text{-Tol})_3$ (entry 3).[21] Electron-rich aryl chlorides illustrated the same trend: the use of PPh_3 and $P(p\text{-Tol})_3$ resulted in higher yields than with $P(o\text{-Tol})_3$, although, as expected, the yields were lower than with activated substrates (entries 5–7). Other triarylphosphines such as $PPh(p\text{-Anisyl})_2$ and $P(p\text{-Anisyl})_3$ were found to be commensurate in their behaviour to PPh_3 and $P(p\text{-Tol})_3$. $Pd(PPh_3)_4$,

Table 1. Heck reactions of aryl bromides using monodentate phosphine ligands

Entry	R^1	R^2	Catalyst	[Pd] (mol%)	P ligand	Pd/P ratio	Temp (°C)	Time (h)	Yield (%)	Reference
1	HO	CO_2Me	$Pd(OAc)_2$	1.0	$P(o\text{-Tol})_3$	1:2	75	22	98	27
2	HO	CO_2Me	$Pd(OAc)_2$	1.0	PPh_3	1:2	75	6[a]	3	27
3	H	CO_2Et	$Pd(OAc)_2$	0.01	$P(o\text{-Tol})_3$	1:4	130	8	68	14
4	H	CO_2Et	$Pd(OAc)_2$	0.01	PPh_3	1:4	130	8	65	14
5	H	$CO_2{}^nBu$	$Pd(OAc)_2$	2.0	$P(o\text{-Tol})_3$	1:4	140	22	99	21
6	H	$CO_2{}^nBu$	$Pd(OAc)_2$	2.0	PPh_3	1:4	140	8	94	21
7	CHO	CN	$Pd(OAc)_2$	0.01	$P(o\text{-Tol})_3$	1:2	130	4	89	14
8	CHO	CN	$Pd(OAc)_2$	0.01	PPh_3	1:4	130	9	84	14
9	CHO	CN	$Pd(OAc)_2$	0.01	P^nBu_3	1:4	130	4	87	14
10	NO_2	CO_2Et	$Pd(OAc)_2$	0.0005	$P(o\text{-Tol})_3$	1:4	130	6	67	14

[a] Yields did not increase with longer reaction times.

Table 2. Heck reactions of aryl chlorides using monodentate phosphine ligands

Entry	R^1	R^2	Catalyst	[Pd] (mol%)	P ligand	Pd/P ratio	Temp (°C)	Time (h)	Yield (%)	Reference
1	CHO	$CO_2{}^n$Bu	$Pd(OAc)_2$	2.0	PPh_3	1:4	150	24	69[a]	21
2	CHO	$CO_2{}^n$Bu	$Pd(OAc)_2$	2.0	P(*p*-Tol)$_3$	1:4	150	24	68[b]	21
3	CHO	$CO_2{}^n$Bu	$Pd(OAc)_2$	2.0	P(*o*-Tol)$_3$	1:4	150	70	33	21
4	CHO	$CO_2{}^n$Bu	$Pd(PPh_3)_4$	2.0	–	–	150	24	69	21
5	MeO	$CO_2{}^n$Bu	$Pd(OAc)_2$	2.0	PPh_3	1:4	150	24	41[a]	21
6	MeO	$CO_2{}^n$Bu	$Pd(OAc)_2$	2.0	P(*p*-Tol)$_3$	1:4	150	24	38[b]	21
7	MeO	$CO_2{}^n$Bu	$Pd(OAc)_2$	2.0	P(*o*-Tol)$_3$	1:4	150	24	25[b]	21
8	MeO	$CO_2{}^n$Bu	$Pd(PPh_3)_4$	2.0	–	–	150	24	33	21
9	MeO	CO_2Me	Pd_2dba_3	1.5	P^tBu_3	1:4	120	24	82	28
10	H	CO_2Me	Pd_2dba_3	1.5	P^tBu_3	1:4	100	42	76	28
11	H	CO_2Me	Pd_2dba_3	1.5	7	1:2.4	100	22	<2%	28

[a] Average yield of three reactions.

[b] Average yield of two reactions; **7**=P[2,4,6-$(CH_3O)_3C_6H_3]_3$.

with no further addition of a ligand, also gave yields in agreement with PPh_3 and P(*p*-Tol)$_3$ (entries 5, 6 and 8).

The issue of aryl scrambling can be eradicated for activated (electron-poor) aryl bromides if the temperature of the reaction is kept below 120°C, or by adopting phosphine-free (Jeffrey's) conditions. The use of deactivated (electron-rich) aryl bromides, however, still results in the formation of scrambled products under these conditions.

Further problems were additionally encountered with the use of aryl chlorides. Both *cis* and *trans* isomers of the cinnamate product were formed in a general ratio of ca. 30:70.[14] Aryl scrambling also became a serious issue, producing appreciable amounts of side products for both activated and deactivated substrates.[21] In all of the examples described, it was calculated that up to 50% of all P–Ar bonds were cleaved for the ligands PPh_3, P(*p*-Tol)$_3$, PPh(*p*-Anisyl)$_2$, P(*p*-Anisyl)$_3$ and $Pd(PPh_3)_4$, and this was attributed to the elevated reaction temperatures (≥140°C).

The well known ligands including PPh_3, P(*o*-Tol)$_3$, BINAP and DPPF, which have proved to be so successful under other circumstances, also resulted in <2% conversion.[30]

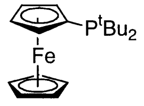
Sterically hindered, electron-rich phosphines have been found to be active for many palladium-catalysed processes in C–X (X=O, S and N) and C–C coupling reactions of aryl halides,[31] even at room temperatures.[32–34] Not surprisingly, when the same ligands were applied to the Heck arylation reaction, it was found that good conversions of previously difficult substrates could be achieved at temperatures well below those normally expected for aryl chlorides.

The use of tri-*tert*-butylphosphine, P^tBu_3, as an effective ligand for the Heck arylation of non-activated aryl chlorides and bromides was reported, independently, by Fu[30] and Hartwig,[35] respectively. Interestingly, $Pd(dba)_2$, instead of the more commonly used $Pd(OAc)_2$, was chosen as the palladium precursor for the systems under study. By using 1 mol% $Pd(dba)_2$–2 mol% P^tBu_3 with an inorganic base (NaOAc) in DMF, 4-bromotoluene and 4-bromoanisole were found to react with n-butyl acrylate in 2 h at 75°C to furnish the corresponding cinnamate ester in 100 and 95% yields, respectively.[35] Under similar conditions (1.5 mol% Pd_2dba_3–6 mol% P^tBu_3 with $CsCO_3$ in dioxane), chlorobenzene and 4-chloroanisole could also be converted to the corresponding methyl cinnamic esters in yields of 82 and 76% at temperatures of 120 and 100°C, respectively (Table 2; entries 9 and 10).[30]

Through an impressive high-throughput screening of ligands for Heck catalysis, the bulky di(*tert*-butylphosphino)ferrocene ligand **6** was found to give excellent conversions for a range of aryl bromides and chlorides,[35] which were converted to the corresponding *n*-butyl cinnamate in >90% yields (Table 3; entries 1–3).

Ligand **6** is the ferrocenyl analogue of Fu's sterically hindered phosphine, P^tBu_3. Application of Fu's optimised conditions with ligand **6** afforded the coupled product of 4-chloroanisole in 80% yield (Table 3, entry 4). Ligand **6**, therefore, is commensurate in its behaviour to P^tBu_3: on performing the same reaction, Fu achieved a yield of 82% (Table 2, entry 9). It was speculated that the electron-rich palladium complex facilitated the oxidative addition of the

Table 3. Heck reactions of aryl bromides and chlorides with catalyst **6**



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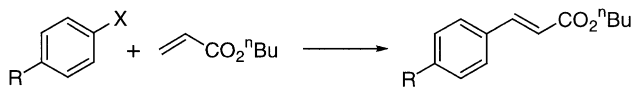
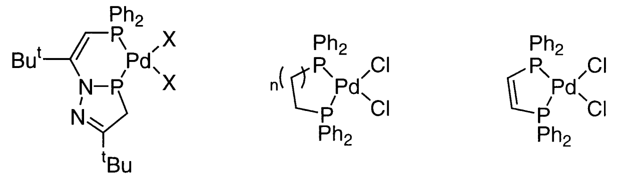


Entry	R	X	Time (h)	Temp (°C)	Yield
1	CO_2Me	Br	2	75	92
2	MeO	Br	2	75	91
3	CO_2Me	Cl	4	110	97
4	MeO	Cl	24	110	80[a]

Conditions: ArX (1 equiv.), *n*-butyl acrylate (1.5 equiv.), $Pd(dba)_2$ (2.5 mol%), ligand **6** (5 mol%), NaOAc (1.5 equiv.), DMF.

[a] Optimised conditions developed by Fu:[30] ArX (1 equiv.), *n*-butyl acrylate (2.1 equiv.), $Pd(dba)_2$ (3 mol%), ligand (6 mol%), Cs_2CO_3 (1.1 equiv.), dioxane.



9a: X = Br
9b: X = Cl

10a: n = 0
10b: n = 1
10c: n = 2
10d: n = 3

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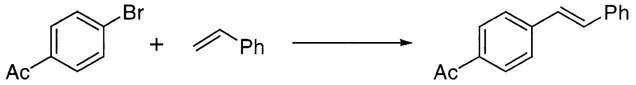
Scheme 6. Preformed diphosphine catalysts.

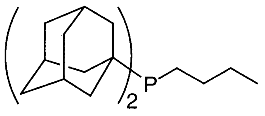
Table 4. Heck reactions of preformed diphosphine catalysts **9–11**



Entry	Catalyst	[Pd] (mol%)	Base	Time (h)	Yield	TON
1	**9b**	3.3×10^{-3}	NBu_3	66	91	27 500
2	**10c**	0.46	NBu_3	24	75	161
3	**10d**	1.5×10^{-2}	NBu_3	24	79	5270
4	**11**	5.2×10^{-2}	$KHCO_3$	24	82	1580

Conditions: ArX (1 equiv.), styrene (1.5 equiv.), base (1.2–1.5 equiv.), 125°C, DMF.

aryl chloride, although the exact mode of action of this novel catalytic system is not known. Perplexingly, the highly basic phosphine ligand, $P[2,4,6\text{-}(MeO)_3C_6H_3]_3$, **7**, which has similar cone angles and pK_a to P^tBu_3,[36] is a poor ligand for the conversion of chlorobenzene to *trans*-methyl cinnamate (Table 2, entry 11). Hartwig et al. speculated that *tert*-butyl ligands could generate higher concentrations of three-coordinated palladium complexes that undergo more facile olefin insertion.[35]



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Beller et al. have reported the activity of bulky di-1-adamantyl-*n*-butylphosphine, **8**, for the Heck reaction of non-activated and deactivated aryl chlorides.[37] Employing Fu's optimized reaction conditions (K_3PO_4; P/Pd=2:1; dioxane) with 1 mol% $Pd(dba)_2$, the reaction of 4-chlorotoluene with styrene proceeded at 120°C in 98% yield. A number of other non-activated aryl chlorides (chlorobenzene and 4-chloroanisole) can also be activated under these conditions to give the desired aryl olefins in substantial yields (60–98%).

3.1.2. Chelating diphosphine ligands.

Chelating ligands such as $(DPPF)_2Pd$ and $(BINAP)_2Pd$ are active catalysts for the activation of aryl bromides and chlorides towards amination reactions[38–40] where the steric bulk of these ligands is found to accelerate the rate of the oxidative addition step.[41,42] These catalysts are not, however, efficient for the Heck reaction with the same aryl species.[30,35]

It is widely accepted that metal complexes containing chelating diphosphines are generally less robust than those containing monodentate phosphine ligands due to the inability of the phosphorus donors to adopt the thermodynamically more stable *trans*-geometry.[8]

An investigation by Shaw revealed that catalysts **9–11** (Scheme 6) could be used to successfully couple electron-poor aryl bromides, although fairly long reaction times were required.[43] On using **9b**, a TON of 27 500 and a yield of 91% could be achieved for the coupling of 4-bromoacetophenone with styrene in 66 h (Table 4; entry 1). For good conversions, larger concentrations of the catalyst were necessary for **10** and **11**; 0.5 mol% of **10c** resulted in a yield of 75% and 0.02 mol% of **10d** in 79% (entries 2 and 3). The palladacycle **11** showed comparable activity to **10a–c** where yields of >80% could be obtained (entry 4).

To date, the only chelating diphosphines successfully applied to the Heck arylation of aryl chlorides have been the electron-rich 1,3-bis(diisopropylphosphino)propane (dippp) and 1,4-bis(diisopropylphosphino)butane (dippb).[28,44–46] The formation of *cis*-stilbene can be achieved in 81% yield using dippp with reducing conditions (Table 5; entry 1). On increasing the temperature to 160°C *cis–trans* isomerism occurs (entries 1 and 2). Electron-withdrawing groups on the aryl chloride influence the formation of the *trans* isomer, where an increase in the temperature is beneficial for this conversion (entry 3). Electron-rich aryl chlorides preferentially form *cis* products but the overall yield is low and a substantial amount of the *trans* isomer is formed (entry 4). Ar–H is always generated as a by-product in varying yields (entries 1–4).

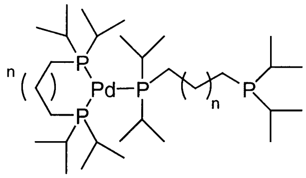
Table 5. Heck reactions of aryl chlorides using chelating ligands dippp and dippb

Entry	P_2 ligand	R	Temp (°C)	Solvent	Yield (*cis*:*trans*) (%)	Yield Ar–H (%)
1	dippp	H	140	DMF	81:7	2
2	dippp	H	160	NMP	48:43	1
3	dippp	CO_2Me	160	NMP	0:65	20
4	dippp	MeO	140	DMF	37:12	12
5	dippb	H	150	DMF	4:80	–
6	dippb	CHO	150	DMF	5:90	–
7	dippb	MeO	150	DMF	2:19	–

Conditions: For dippp-$Pd(OAc)_2$ (1 mol%), dippp (2 mol%), Zn, Ar, 24 h. For dippp-$Pd(OAc)_2$ (1 mol%), dippb (2 mol%), NaOAc, Ar, 24 h.

Under basic conditions with dippb, 80% of *trans*-stilbene is formed (entry 5). Excellent yields and selectivities for the *trans* product can be achieved for activated aryl chlorides (entry 6), and while a continuing preference for the *trans* isomer is maintained, deactivated aryl chlorides still result in low conversions (entry 7). No catalyst decomposition and formation of palladium black was observed for reactions under basic conditions.

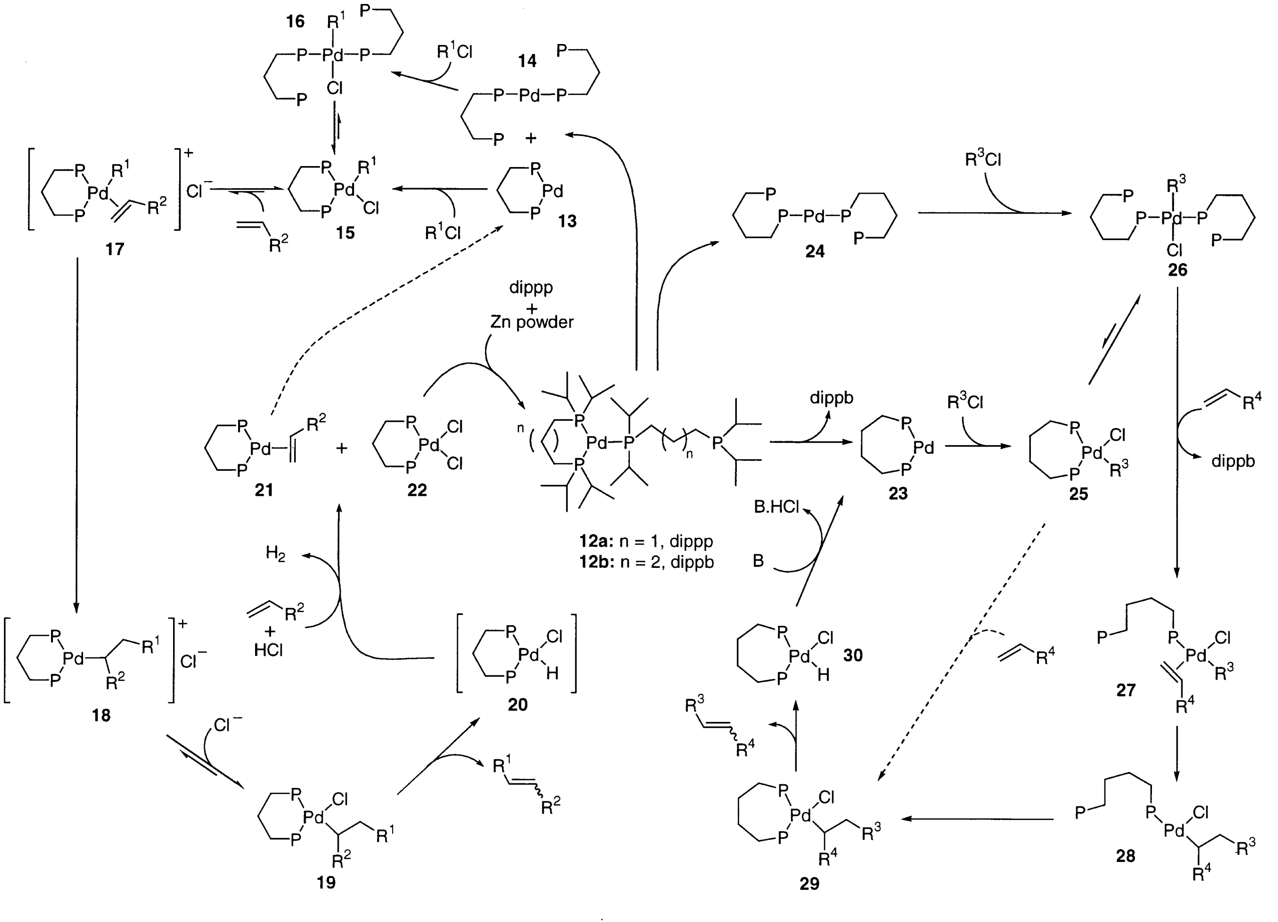
$\mathrm{Pd(dippp)_2}$ **12a** and $\mathrm{Pd(dippb)_2}$ **12b** are trigonal complexes where one diphosphine ligand exists as a bidentate ligand and the other as a monodentate ligand.



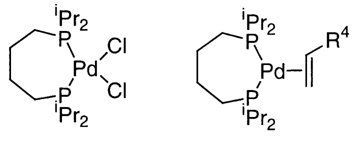
12a: n = 1, dippp
12b: n = 2, dippb

Complex **12b** is an active catalyst for the coupling of aryl chlorides with styrenes under normal Heck reaction conditions, giving predominantly *trans* products.[44] Intriguingly, its analogue **12a** was found to act as a catalyst under reducing conditions, i.e. in the presence of zinc.[46] Detailed experiments revealed that **12a** operated via a cationic route and **12b** via a neutral pathway. In the following discussion, the role of $\mathrm{Pd(dippp)_2}$ **12a** and then $\mathrm{Pd(dippb)_2}$ **12b** will be considered in the Heck reaction.[28,45]

For the oxidative addition of aryl halides to occur, it is possible for complex **12a** to generate two coordinatively unsaturated 14-electron complexes **13** and **14** (Scheme 7). Inversion transfer NMR spectroscopy has demonstrated the existence of **13**, the major species, and while **14** was not observed directly, the identification of other complexes later in the pathway supports its existence. Complexes **13** and **14** undergo oxidative addition of R^1Cl to give *cis*-(dippp)Pd(R^1)Cl **15** and *trans*-(η^1-dippp)$_2$Pd(R^1)Cl **16**. The rate of oxidative addition to **13** is appreciably faster than to **14** due to the smaller P–Pd–P bite angle of **13**. Equilibrium between **15** and **16** lies in favour of the *cis* complex as a result of the stabilising energy that the six-membered chelate provides. A vacant coordination site is made available by the deligation of the halide ligand, and the coordination of the alkene ensues (**17**). In doing so, the mechanism switches from a neutral to a cationic pathway. Migration of R^1 (**18**), the reaffiliation of Cl^- (**19**) and β-hydride elimination generates *cis*-(dippp)Pd(H)Cl **20** an unstable complex which was not observed directly, but has been proposed to undergo immediate disproportionation to give a 1:1 mixture of **21** and **22**. Complex **21** is catalytically active and can re-enter the cycle. Complex **22** is catalytically inactive and will remain in this form unless the reaction is carried out under reducing conditions. In the presence of excess dippp and zinc powder, **22** is converted into **12a**



Scheme 7. Mechanistic pathways of $\mathrm{Pd(dippp)_2}$ **12a** and $\mathrm{Pd(dippb)_2}$ **12b**, ^{i}Pr groups have been removed for clarity.



31 32

Scheme 8.

which is then able to re-enter the cycle. If the reaction is carried out under basic conditions, every turn of the cycle leads to 50% of the remaining catalytic species being trapped as inactive **22**.

The Pd(dippp)$_2$ system generally forms *cis* alkene products. Palladium hydride species were purported to promote the *cis–trans* isomerism. In the dippp mechanism, *cis*-(dippp)Pd(H)(Cl) **20** is thought to have a very short lifetime and thus, does not exist long enough to convert *cis* alkenes to the *trans* form.

The mechanistic pathway adopted by the Pd(dippb)$_2$ complex is subtly different. As with **12a**, complex **12b** also forms *cis* and *trans* coordinatively unsaturated 14-electron species **23** and **24** (Scheme 7). Oxidative addition of R^3Cl generates *cis*-(dippb)Pd(R^3)Cl **25** and *trans*-(η^1-dippb)$_2$Pd(R^3)Cl **26**, as expected. Complexes **25** and **26**, however, have similar rates of formation, since the stabilising energy of the seven-membered dippb chelate is less than that of the six-membered dippp chelate. An equilibrium exists between **25** and **26**, which now lies in favour of the *trans* complex **26**, in contrast to the dippp analogues. Loss of a ligand creates a vacant coordination site for subsequent ligation of the alkene, $H_2C{=}CHR^4$, generating the neutral complex **27**. Alkene insertion (**28**) is promoted by chelate formation (**29**) and this ring-opening and ring-closing ability of the diphosphine ligand is characteristic of Pd(dippb)$_2$. β-Hydride elimination then ensues, furnishing complex **30**. It was noted that the use of a secondary or tertiary amine did not regenerate the active catalytic species **23**. Instead, *cis*-(dippb)PdCl$_2$ **31** and *cis*-(dippb)Pd(η^2-$H_2C{=}CHR^4$) **32** (Scheme 8) were created through the disproportionation of complex **30**. Sodium acetate was, however, found to suppress the formation of the dichloride complex **31**, thus enabling palladium species **30** to re-enter the catalytic cycle.

As the palladium hydride complexes of the dippb ligand have longer lifetimes, they can catalyse the *cis–trans* isomerisation and the neutral pathway thus favours the formation of *trans* (thermodynamic) alkenes.

Insertion and migration of the alkene from complex **25** to give complex **29** can occur. The mechanism follows the cationic pathway given for Pd(dippp)$_2$. As the existence of this route is undesirable, it can be suppressed through the addition of chloride ions or the use of a less polar solvent.

3.1.3. Phosphite ligands.

A standard approach to ligand development has been to create palladium complexes coordinated by electron-rich phosphines. For this reason, electron-poor phosphites have been somewhat excluded as potential ligands, although they are generally cheaper and easier to generate.

Early work by Spencer[29] used the readily available P(OPh)$_3$ (Pd/P=1:4) to test the efficacy of these ligands in Heck reactions with aryl bromides. Although 4-bromobenzaldehyde afforded 85% yield on coupling with acrylonitrile (Table 6; entry 1), only 11% of product was obtained from the reaction of bromobenzene with ethyl acrylate (entry 2). When the system was revisited by Beller and Zapf in 1998,[47] the application of large excesses of triaryl- and trialkylphosphites was found to lead to good yields. Deactivated 4-bromoanisole reacted with styrene to give 66% *trans*-methyl 4-methoxycinnamate when a [Pd(OAc)$_2$+P(OEt)$_3$] catalytic combination was used (Table 6; entry 3). Very low concentrations of the palladium catalyst can be used, resulting in large TONs: 4-bromoanisole reacted to give the corresponding cinnamic ester with only 0.001 mol% of Pd(OAc)$_2$. The TON was large (31 000) but the final yield of product was low (entry 4).

Although phosphites are generally more widely available than phosphines, their use has some serious drawbacks. Firstly, an appreciable amount of tetra-*n*-butylammonium bromide additive is required. Secondly, optimum conditions were only achieved when excesses of the trialkyl (100-fold) or triaryl (10-fold) phosphite ligands were applied. This was attributed to hydrolytic instability and the weaker binding ability of phosphites compared to phosphines. Overall, the discovery of the phosphite systems is an obvious advancement in Heck chemistry. Further developments are, however, needed before the less activated aryl chlorides can react.

3.1.4. Phosphonium salts.

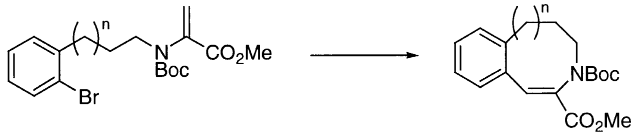
In Section 2.2, phosphonium salts were found to be involved in the formation of unwanted by-products through aryl scrambling. Since addition and elimination is a reversible process, it is,

Table 6. Heck reactions of aryl bromides using phosphite ligands

Entry	R^1	X	R^2	Pd catalyst	Mol%	P ligand	Pd/P ratio	Temp (°C)	Time (h)	Yield (%)	Reference
1	CHO	Br	CN	Pd(OAc)$_2$	0.01	P(OPh)$_3$	1:4	130	6.5	85	29
2	H	Br	CO$_2$Et	Pd(OAc)$_2$	0.01	P(OPh)$_3$	1:4	130	8	11	29
3	MeO	Br	Ph	Pd(OAc)$_2$	–	P(OEt)$_3$	[a]	140	24	66	47
4	MeO	Br	Ph	Pd(OAc)$_2$	0.001	P(O-2,4-^{t}Bu$_2$C$_6$H$_3$)$_3$	1:10	140	24	31	47

Ratio of Pd/P/Bu$_4$NBr=1:100:200.

[a] Ratio of Pd/P/Bu$_4$NBr=1:10:200.



33a: n = 1
33b: n = 2

34a: n = 1, 58%
34b: n = 2, 69%

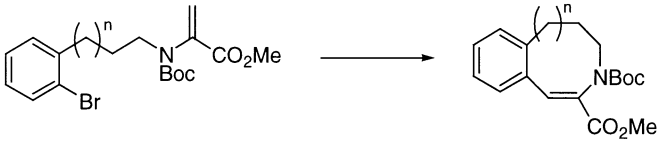
Scheme 9. Cyclisation of challenging aryl bromides; conditions: Pd(OAc)$_2$ (5 mol%), PPh$_4$Cl (30 mol%), NaOAc, DMF, Ar.

perhaps, not surprising that the phosphonium iodide salts (RPh$_3$P$^+$I$^-$, R=Me or Ph) can be used stoichiometrically as a source of aryl iodide in the Heck reaction.[26] This was later developed by Reetz to activate aryl bromides and chlorides, through the use of catalytic quantities of tetraphenylphosphonium salts (PPh$_4$X; X=I, Br or Cl).[48] Aryl scrambling was found to be a feature of the system, but the addition of *N*,*N*-dimethylglycine (DMG) [Pd(II) salt/PPh$_4$Cl/DMG=1:6:6] could limit the extent of P–C bond cleavage. Under these conditions, the Heck reaction of chlorobenzene with styrene proceeded at 150°C with 2 mol% of the Pd catalyst to give predominantly *trans*-stilbene. Reactions of bromobenzene and *p*-bromoanisole with acrylates also proceeded with 97 and 71% yields, with TONs of 9800 and 1300, respectively. The role of DMG additive is uncertain.

Reetz's approach was recently applied to an intramolecular cyclisation, where the transformation of **33a** and **33b** to **34a** and **34b** could be achieved in overall yields of 58 and 69%, respectively (Scheme 9),[49] with no detectable aryl scrambling products.

An attempt to cyclise **33b** using Jeffrey's conditions at 110°C resulted in a poor yield of **34b** (4%) with the recovery of 77% of the starting material (Table 7; entry 1). Increasing the temperature to 150°C, led to a similar yield with a lower recovery of starting material (entry 2). Less than 1% cyclisation took place in a test reaction where PPh$_4$Cl was excluded (entry 3), indicating the importance of this additive in these intramolecular reactions.

Table 7. Intramolecular cyclisation reaction employing tetraphenylphosphonium salts



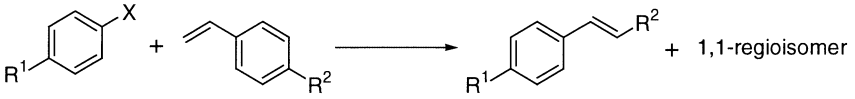
33b: n = 2

34b: n = 2

Entry	Pd(OAc)$_2$ (mol%)	Base	Other	Temp (°C)	Time (h)	Recovered **33b** (%)	Yield **34b** (%)
1	2.5	NaHCO$_3$	^{n}Bu$_4$NCl (1 equiv.), 4 Å MS	110	16	77	4
2	2.5	NaHCO$_3$	^{n}Bu$_4$NCl (1 equiv.), 4 Å MS	150	16	27	6
3	5	NaOAc	No PPh$_4$Cl	120	0.5	51	<1
				150	4		

All reactions were carried out under an inert atmosphere of N$_2$ or Ar.

Table 8. Heck reaction of aryl halides using a heterogeneous clay catalyst

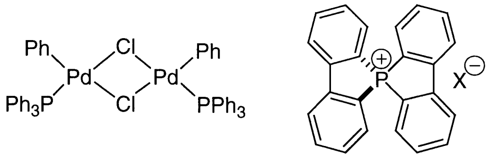


Entry	R^1	X	R^2	Time (h)	Yield (*trans*) (%)	Yield (1,1) (%)
1	H	I	H	2	95	5
2	CHO	Br	H	3	98	2
3	CHO	Br	MeO	25	98	2
4	CHO	Cl	H	36	61^a	2^a

Conditions: Clay catalyst, NaOAc, DMF, 140°C.
[a] Products lacking 4-CHO functionality.

Palladium chloride and tetraphenylphosphonium bromide have been successfully incorporated into montmorillonite K10 clay to produce a recyclable heterogeneous catalyst.[50] This catalyst exhibited good activity for the coupling of iodobenzene and 4-bromobenzaldehyde with styrene derivatives (Table 8; entries 1–3). The one example given of an aryl chloride, 4-chlorobenzaldehyde, however, resulted in the formation of stilbene with loss of the aldehyde functionality (entry 4).

A detailed mechanistic account of the system has not yet been provided but as the formation of palladium black is minimal, it was suspected that a palladacycle, or its



35

36: X = I, Cl

Scheme 10.

monomer, could be involved (cf. Section 3.2). The palladacycle **35** (Scheme 10), a possible in situ candidate, was duly synthesised and was found to be both thermally stable and active in catalysis with added PPh_4Cl (chlorobenzene and styrene, 150°C, NMP, 12 h, 86% conversion). Significantly, the use of the phosphonium salt **36** was unsuccessful in catalysis and Reetz attributes this to the fact that this salt is very stable and cannot undergo ring-opening arylation.

3.2. Palladacycles

3.2.1. P–C Ligands

3.2.1.1. Cyclometalated phosphine ligands. The effectiveness of tri-*o*-tolylphosphine in the Heck reaction has been known for a long time, but until the pioneering work of Herrmann, its effects in situ were attributed to the steric bulk of the *ortho* substituents.

On reaction with palladium(II) acetate, the tri-*o*-tolylphosphine undergoes a cyclometalation reaction at one of the *ortho*methyl groups to generate complex **37**.[51] In solution, di(μ-acetato)-bis[*o*-(di-*o*-tolylphosphino)benzyl)] palladium(II) **37** (which has since become known as Herrmann's catalyst) and the dimeric complex **39** are in equilibrium with their monomeric forms **38**, **40** and **41** (Scheme 11). The addition of halide ions (e.g. through catalysis or by addition of Bu_4NX) converts **37** to **39** through the exchange of the weakly bound acetate bridges.[52]

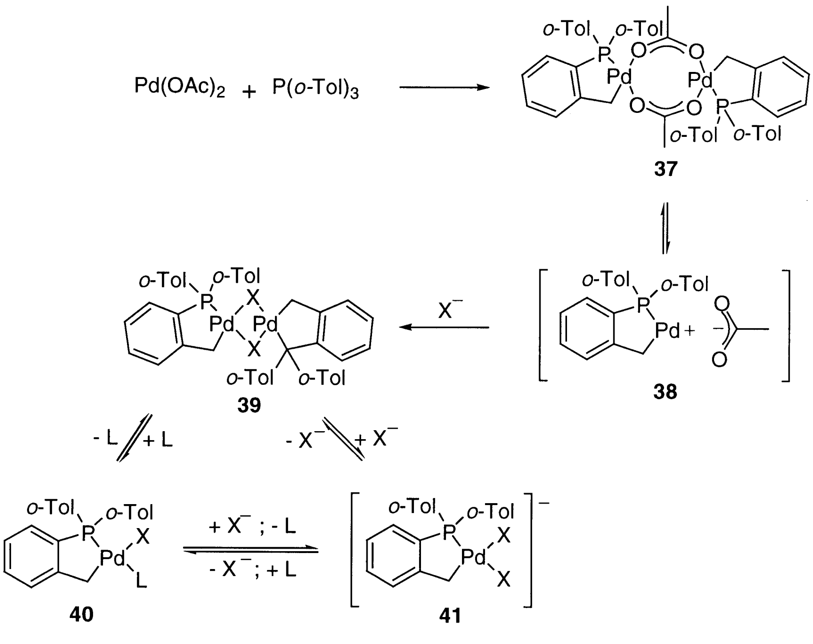
Palladacycles **39a** (X=I) and **39b** (X=Br) have been isolated by Heck as by-products in reactions of aryl iodides and bromides with conjugated dienes.[53] He found the pure dimeric species **39a** was unable to catalyse diene arylation unless the additive, tetraethylammonium iodide, was added to the reaction mixture.

Palladacycles **37** and **39** exhibit a number of distinctive characteristics—(a) they are very thermally stable, with decomposition temperatures above 250°C, (b) the catalysts become active at temperatures above 80°C and the formation of palladium black, which is a feature of many Heck reactions, occurs rarely and in trace amounts, (c) the complications associated with P–C bond cleavage can also be circumvented, as the generation of scrambled by-products does not occur until reaction temperatures exceed 165°C; and (d) the catalysts are extremely active, more so than the in situ catalysts of $[Pd(OAc)_2{+}n\ P(o\text{-Tol})_3]$, and are ideal candidates for the transformations of challenging substrates such as aryl chlorides.[52]

Extremely good conversions can be obtained for aryl bromides (Table 9; entry 1).[54] 4-Bromoacetophenone can be converted to the corresponding cinnamic ester using very low concentrations of catalyst, and TONs of 10^6 can be achieved in the presence of the additive, Bu_4NBr (entry 2). Classic in situ conditions can also realise TONs of 10^6 (entries 3 and 4).

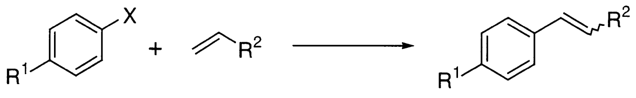
Deactivated aryl bromides require higher reaction temperatures and greater concentrations of catalyst to achieve good conversions. Utilising 2 mol% of **37** at 140°C, 4-bromoanisole can be reacted to afford 94% of the coupled product (entry 5). In comparison, a 1:1 mixture of palladium(II) acetate and tri-*o*-tolylphosphine gave a poorer yield of 75% after heating for 93 h (entry 6).

The sole use of Herrmann's catalyst gave disappointing results for activated aryl chlorides with the formation of palladium black at 120°C (entry 7).[55] The addition of alkali metal salts e.g. LiBr or tetra-*n*-butylammonium bromide, however, accelerated the conversion to give excellent yields (entry 8). The extra stability conferred by the addition of halide ions is presumed to be due to the formation of anionic complexes that are more active than their neutral counterparts. The addition of tetraphenylphosphonium chloride also resulted in extremely good conversions (entries 9 and 10),



Scheme 11. X=I, Br, Cl; L=Ligand e.g. DMF, CH_3CN, pyridine, phosphines.

Table 9. Heck reactions of aryl bromides and chlorides using palladacycles **37**, **42** and **43**



Entry	R^1	X	R^2	Catalyst	Mol%	Other (mol%)	Temp (°C)	Time (h)	Yield (%)	TON	Reference
1	CHO	Br	$CO_2{}^nBu$	**37**	1.0	–	100	2	>99	100	54
2	COPh	Br	$CO_2{}^nBu$	**37**	0.0001	Bu_4NBr (20)	130	24	>99	10^6	54
3	COPh	Br	$CO_2{}^nBu$	$Pd(OAc)_2$	0.0001	PPh_3 (0.0002) Bu_4NBr (20)	130	24	>99	10^6	54
4	COPh	Br	$CO_2{}^nBu$	$Pd(OAc)_2$	0.0001	P(*o*-Tol)$_3$ (0.0002) Bu_4NBr (20)	130	24	>99	10^6	54
5	MeO	Br	$CO_2{}^nBu$	**37**	2.0	–	140	48	94	47	54
6	MeO	Br	$CO_2{}^nBu$	$Pd(OAc)_2$	1.0	P(*o*-Tol)$_3$ (1)	140	93	75	75	54
7	CHO	Cl	$CO_2{}^nBu$	**37**	2.0	–	140	24	12	6	55
8	CHO	Cl	$CO_2{}^nBu$	**37**	0.2	Bu_4NBr (20)	130	24	81	405	55
9	NO_2	Cl	Ph	**37**	0.1	PPh_4Cl (1)	140	60	91[a]	910	55
10	H	Cl	Ph	**37**	2.0	PPh_4Cl (12)	150	41	97	49	55
11	MeO	Cl	Ph	**37**	0.2	PPh_4Cl (1)	150	60	38[b]	190	55
12	COMe	Br	Ph	**42**	2.6	–	125	7	94	180	56
13	CN	Br	Ph	**42**	2.6	–	125	7	85	165	56
14	H	Br	Ph	**43**	0.1	–	115	30	77	770	56

[a] Stilbene formed as a by-product.

[b] Equivalent yield of stilbene produced.

but P–C bond cleavage and aryl scrambling ensue at these high reaction temperatures. Extensive by-products are formed on reaction of the deactivated 4-chloroanisole (entry 11).

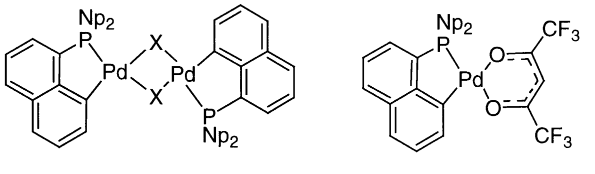
Complex **37** has been applied to the synthesis of steroids[57] and cephalotaxine,[58] the preparation of the anticoagulant, DX-9065a,[59] and the formation of benzofurans.[60]

Palladacycles **42** and **43** (Scheme 12), which are structurally similar to Herrmann's P(*o*-Tol)$_3$ palladacycles, have been developed by Shaw[56] and were found to catalyse the reactions of activated aryl bromides (Table 8; entries 12, 13 and 14). No additives were used, so the TONs were not as high as the Bu_4NBr-promoted reactions of Herrmann but, nevertheless, reasonable to excellent yields were obtained.

No examples of aryl chloride couplings were given, and if comparisons can be drawn between **42** and **43** and Herrmann's catalysts, it might be predicted that they are virtually inactive without the presence of a promoter.

3.2.1.2. Pd(0)/Pd(II) or Pd(II)/Pd(IV) mechanism?

The apparent stability of the cyclopalladated complexes at high temperatures has led to numerous speculations on their precise mode of action in Heck reactions. A proposed mechanism involving Pd(II)/Pd(IV) reaction intermediates was supported by the fact that Pd(IV) complexes are known to be stable under certain reaction conditions.[61] Oxidative addition of an alkyl halide to a cyclometalated palladium(II) complex (**44** to **47**) has also been reported by Catellani (Scheme 13), albeit under rather special circumstances, namely that competitive *syn* β-hydride elimination cannot occur.[62–65]



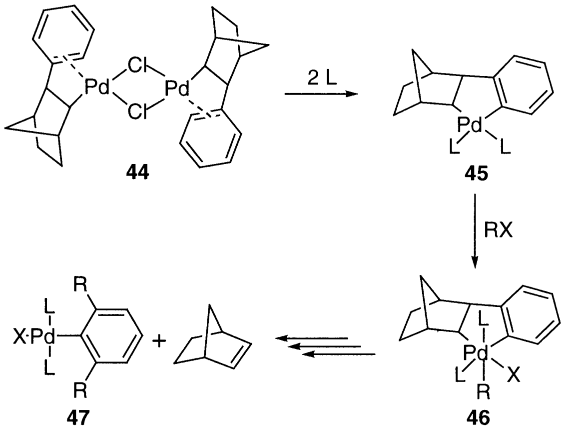
42: X = OAc

43

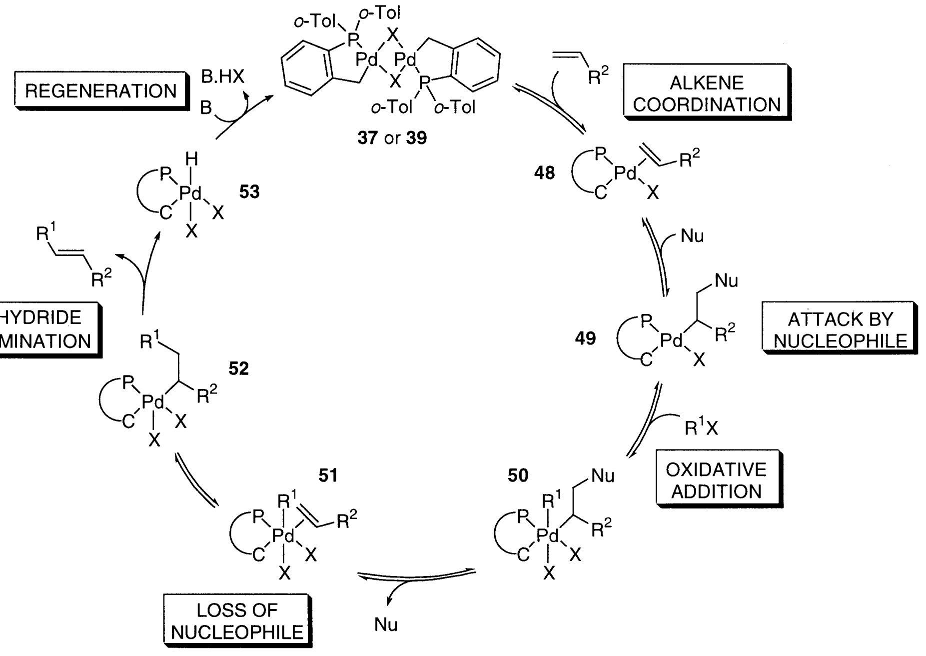
Scheme 12. Shaw's palladacycles; Np=naphthyl.

Herrmann has reported that oxidative addition of the aryl bromides was only observed upon alkene addition, implying that the rate-determining step is the coordination of the alkene.[52,55] The only species detected in situ using NMR spectroscopy, however, were Herrmann's catalyst **37**, palladacycle **39** and the monomeric complexes **40** and **41**. No formation of Pd(0) species was evident and intermediary Pd(IV) complexes or oxidised by-products of any kind were not detected. The operation of a Pd(II)/Pd(IV) mechanism was, however, suggested.

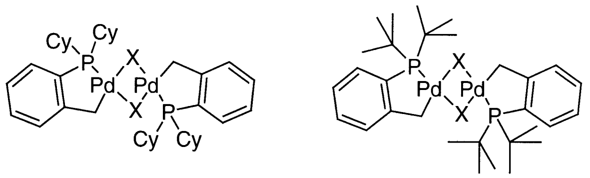
A catalytic cycle involving higher oxidation states of palladium was also favoured by Shaw based largely on known organoplatinum chemistry (Scheme 14).[56,66] The proposed catalytic cycle begins with the coordination of the alkene to form complex **48**. The coordinated alkene then undergoes a reversible attack by a nucleophile e.g. the base, and is converted into a σ-donor ligand. Complex **49** (which can have an overall negative charge if the nucleophile is charged) is now sufficiently electron rich to



Scheme 13. Pd(IV) intermediate formation; R=alkyl, benzyl; X=I, Br; L=DMF, methyl isonicotinate.



Scheme 14. Shaw's Pd(II)/Pd(IV) mechanism; R^1=Ar; X=I, Br, Cl; X=AcO, Br, Cl; Nu=AcO^-, OH^-, Br^-, I^-, amines etc.



54 **55**

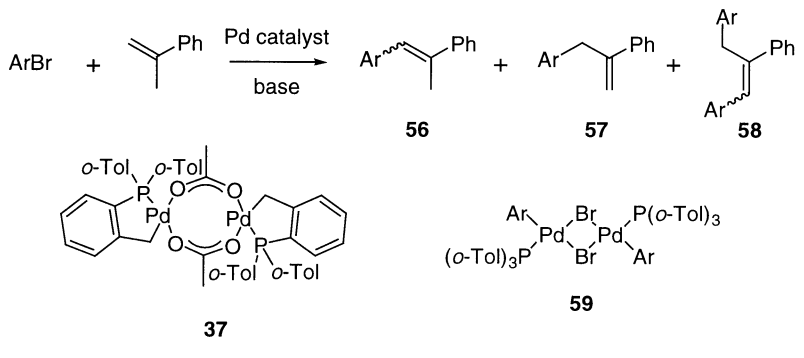
Scheme 15. X=AcO, I, Br; Cy=cyclohexyl.

oxidatively add R^1X, forming the Pd(IV) intermediate (**50**). Loss of the nucleophile restores the alkene (**51**) where migration of R^1 (**52**), followed by β-hydride elimination, creates the Pd–H complex **53**. Regeneration of the catalyst is effected through the base-promoted removal of HX.

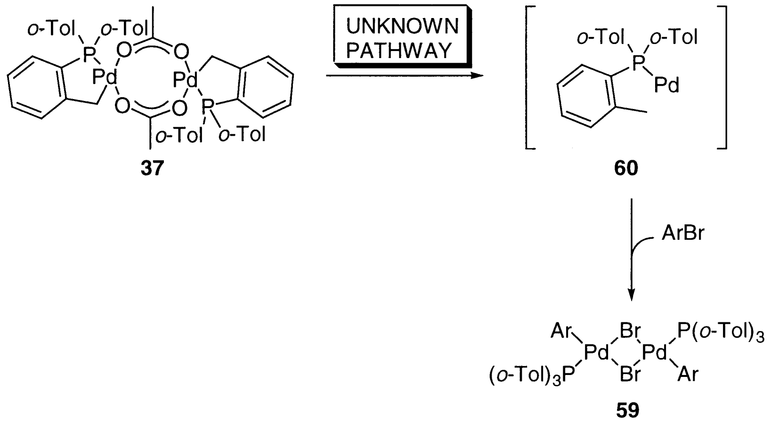
In Shaw's conjecture, the σ-donor substituents are envisaged to be important. The mechanism involves the rate-determining, reversible, attack of the nucleophile to give the σ-alkyl complex (**49**). With two alkyl substituents and an electron-rich phosphine ligand, complex **49** is sufficiently electron-rich to oxidatively add R^1X. Increasing the donor ability of the phosphine ligands should therefore facilitate the activity of the palladacycle. The duly synthesised palladacycles **54** and **55** (Scheme 15) were, however, found to be less active than their aryl counterparts.[55]

Contradictory experimental evidence against the proposed Pd(II)/Pd(IV) catalytic cycle was also uncovered.[67] During a study of the coupling reactions of various aryl bromides with 1,2-disubstituted olefins with phosphapalladacycle **37** as the catalyst, the reaction of 1-bromo-4-chlorobenzene and α-methylstyrene gave **56**, **57** and **58** in a ratio of 35:61:4 (Scheme 16). Complex **59** was isolated from the reaction mixture, and was envisaged as a dimeric intermediate formed from the oxidative addition of ArBr to a Pd(0) intermediate **60**, generated via an unknown metalacycle ring opening of **37** (Scheme 17). When the isolated complex **59** was applied to the reaction, the initial rates of formation of **56**, **57** and **58** significantly increased, giving a similar isomer distribution of these compounds. This led to the hypothesis of a reduction and subsequent oxidative addition of the catalyst precursor, forming palladium(0) as the active catalytic intermediate.

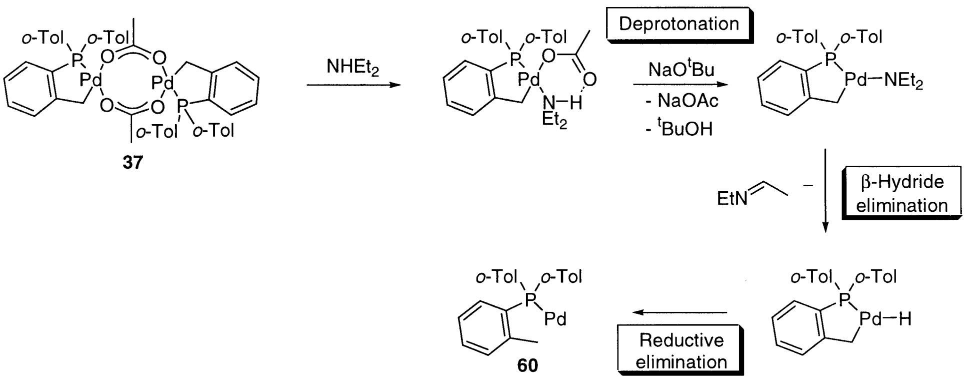
The reduction of complex **37**–**60** probably proceeds through a heterolytic Pd–C bond cleavage, but the precise pathway is unclear. Previously studies carried out by Hartwig on the



Scheme 16. Ar=4-ClC_6H_4.



Scheme 17.

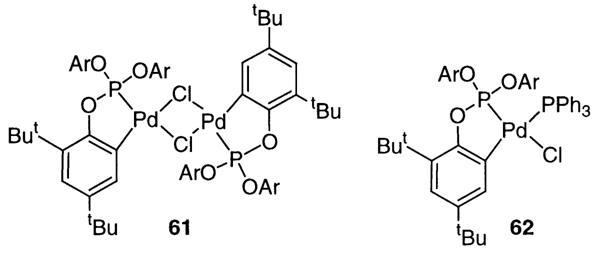


Scheme 18. Hartwig's reduction pathway.

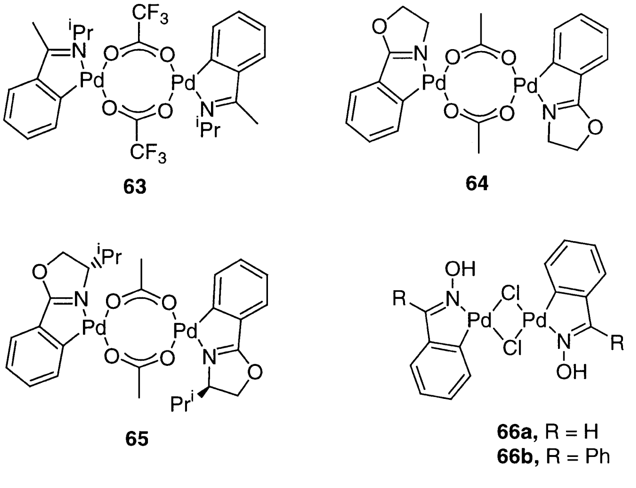
mechanism of aryl amination reactions[68] revealed that this reduction can indeed occur in the presence of amine and a strong base (Scheme 18). Further studies need to be undertaken, however, in order to ascertain the reductive pathway to **60** under conditions adopted in Heck reactions, and whether a Pd(II)/Pd(IV) side mechanism may operate competitively.

In conclusion, it is reasonable to assume that, if palladacycles act through a Pd(0)/Pd(II) mechanism, **60** would have to be an extremely active complex that is present in, as yet, undetectable concentrations.

3.2.1.3. Cyclometalated phosphite ligands. Palladacycles **61** and **62** (Scheme 19) have been synthesised using phosphite ligands.[69] While triarylphosphite ligands are generally less air sensitive than their phosphine cousins, these palladacycles are not as efficient in catalysis as the phosphine palladacyles **37**, **42** and **43** in Heck reactions of aryl bromides. Whilst a TON of 5.75 million was obtained for the vinylation of 4-bromoacetophenone with styrene, the reaction conditions were harsh (180°C for 69 h), resulting in a poor yield of the Heck product (58%) and substantial formation of polystyrene. Complex **61** was also found to be effective for the coupling of electron-rich 4-bromoanisole or bromobenzene with butylacrylate with TONs of up to several hundreds at >140°C, but these reactions are



Scheme 19. Cyclometalated phosphite ligands; Ar=2,4-^{t}Bu$_2$C$_6$H$_3$.



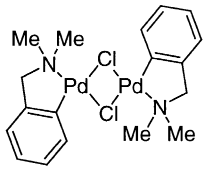
Scheme 20. Cyclometalated imine catalysts **63**–**65** and oxime catalyst **66**.

Table 10. Heck reactions of cyclometalated imine and oxime catalysts

Entry	R	Catalyst	[Pd] (mol%)	Base	Temp (°C)	Time (h)	Yield (%)	TON
1	CO_2Me	**63**	7.0×10^{-5}	Na_2CO_3	140	43	96	137 100
2	CO_2Me	**64**	1.4×10^{-3}	Na_2CO_3	140	130	93	66 400
3	CO_2Et	**66a**	7.2×10^{-4}	K_2CO_3	150	37	52	72 000
4	CO_2Et	**66b**	0.2	K_2CO_3	150	1	90	437
5	Ph	**66a**	6.7×10^{-4}	K_2CO_3	150	48	52	78 000
6	Ph	**66b**	0.2	K_2CO_3	150	1	96	483

Conditions: ArX (1 equiv.), alkene (1.2–1.4 equiv.), base (0.7–1.1 equiv.), NMP or DMF.

Table 11. Heck reaction of cyclometalated amine catalyst **67**



67

Entry	R^1	R^2	Catalyst	[Pd] (mol%)	Base	Temp (°C)	Time (h)	Yield	TON
1	$COCH_3$	$CO_2{}^nBu$	**67**	0.2	NaOAc	140	20	100	500
2	H	CO_2Et	**67**	3.4×10^{-2}	K_2CO_3	150	34	90	2647
3	H	Ph	**67**	1×10^{-4}	K_2CO_3	150	29	87	86 666

Conditions: ArX (1 equiv.), alkene (1.2–1.4 equiv.), base (0.7–1.1 equiv.), NMP or DMF.

markedly more sluggish. No examples of aryl chloride activation were given.

3.2.2. C–N Ligands. Cyclometalated imine catalysts **63–65** (Scheme 20), developed by Milstein, exhibit the air, moisture and thermal stabilities of palladacycles.[70] TONs of >130 000 can be achieved for the coupling of methyl acrylate with bromobenzene resulting in yields >90% (Table 10; entries 1 and 2).

The structurally similar oxime-based palladacycles **66a**,**b** were also reported to exhibit good catalytic behaviour in the coupling reaction of bromobenzene with ethyl acrylate and styrene (entries 3–6).[71]

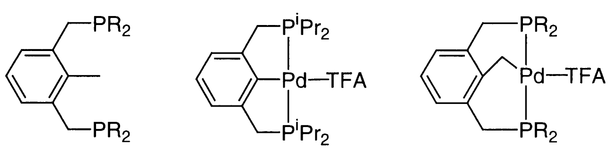
Cyclometalated amine catalyst **67** was reported to lead to a quantitative conversion of 4-bromoacetophenone to the cinnamate ester.[69] Extensive catalyst decomposition was, however, observed during the reaction (Table 11, entry 1), which prevented its further development as a Heck catalyst. The catalyst has been reported by Iyer[71] to be active for the coupling of bromobenzene with ethyl acrylate and styrene in good yields and respectable TONs (entries 2 and 3).

3.3. Tridentate PCP pincer palladacycles

3.3.1. Phosphinato complexes. Milstein's tridentate PCP palladacycles **69** and **70** (Scheme 21) have been synthesised via C–C and C–H bond activation of the diphosphine ligand **68** with $Pd(TFA)_2$.[72] The catalysts are not air sensitive and reactions can be carried out under aerobic conditions. The complexes **69** and **70** are also very stable thermally, decomposing at temperatures >180°C. During catalysis, the formation of palladium black is minimal and ligand exchange of TFA takes place with the corresponding halide.

Respectable TONs can be achieved for aryl bromides (Table 12; entries 1 and 2) but the complexes are inactive for aryl chlorides. No information on the promotional effect of additives such as Bu_4NBr or PPh_4Cl with these catalysts was given. The two examples of aryl bromide coupling presented are interesting as the more 'activated' 4-bromobenzaldehyde reacted to give the cinnamic ester in poorer yield than the bromobenzene vinylation, which seems to contradict the trend exhibited by other catalysts.

3.3.2. Phosphinito complexes. The PCP phosphinito pincer catalyst **72** reported by Jensen is also not air or moisture



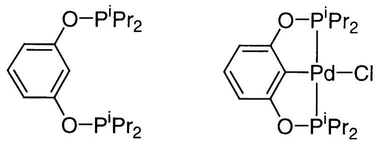
68 **69** **70a:** R = ^{i}Pr
70b: R = ^{t}Bu$_2$

Scheme 21. Milstein's PCP palladacycles.

Table 12. Heck coupling of aryl bromides with Milstein's catalyst **70a**

Entry	R	Catalyst	Mol%	Temp (°C)	Time (h)	Yield	TON
1	H	**70a**	0.7	140	63	93	132 900
2	CHO	**70a**	0.7	140	63	79	113 300

Conditions: ArBr (1 equiv.), alkene (1.2 equiv.), palladacycle **70a**, Na_2CO_3 (1 equiv.), NMP.



71 **72**

Scheme 22. Jensen's PCP palladacycle.

Table 13. Heck coupling of aryl chlorides with Jensen's catalyst **72**

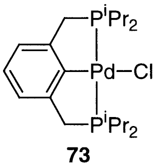
Entry	R	Yield (%)
1	4-MeCO	>99
2	H	>99
3	4-MeO	88
4	2-MeO	85

Conditions: ArCl (1 equiv.), styrene (2 equiv.), **72** (0.67 mol%), CsOAc (1.1 equiv.), dioxane, 120°C (120 h) or 180°C (24 h).

sensitive and is thermally stable (Scheme 22). This complex has proven very successful in activating aryl chlorides,[73] and displays a number of advantages in the activation of these challenging substrates over other systems. Additives or promoters are not required and so complications such as aryl scrambling are avoided, and notoriously difficult aryl chlorides can be transformed efficiently to the *trans* Heck product.

Preparative scale reactions of 4-chloroanisole and 4-chloroacetophenone with styrene were performed with this system. Quantitative conversions were achieved for activated aryl chlorides (Table 13, entries 1 and 2) and impressive yields were additionally attainable for both electron-rich and sterically hindered electron-rich substrates (entries 3 and 4).

Rather interestingly, complex **72** is also found to be highly efficient for the coupling of bromobenzene with styrene to yield exclusively trisubstituted, triphenylethene (7×10^{-4} mol% catalyst). Trisubstituted alkenes were also obtained in good yields by the reaction of bromobenzene with 1,1-disubstituted alkenes (α-methylstyrene and *n*-butyl methacrylate).[74]



73

Scheme 23.

To investigate the catalytic properties of **72**, the phosphinato catalyst **73** was synthesised (Scheme 23) and its reactivity studied. Significantly, **73** showed little activity, and so the enhanced ability of **72** to activate aryl chlorides may be attributed to the phosphinito ligand.

3.3.3. Pd(0)/Pd(II) or Pd(II)/Pd(IV) mechanism?

Milstein discounted a Pd(0)/Pd(II) pathway based on studies carried out with possible reaction intermediates which were isolated or independently prepared. These studies were, however, carried out with aryl iodides and therefore may not adequately represent the true mechanism of the reactions with aryl bromides.[72]

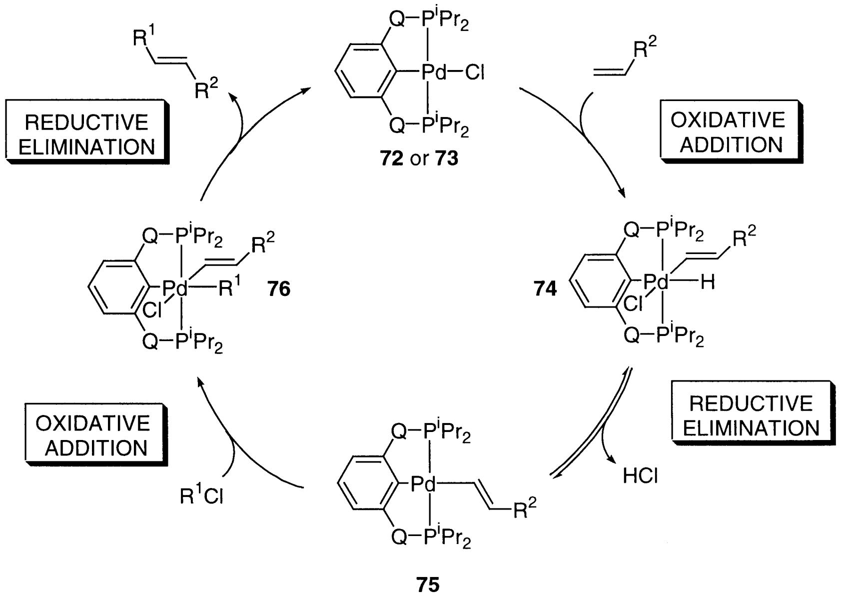
Indeed, Beletskaya and Cheprakov[6] have suggested that phosphine ring-opening may well be a possibility due to the high reaction temperatures, allowing reduction of the monocarbopalladate to a Pd(0) species. As the reactions were carried out aerobically, they propose that air helps to reoxidise the Pd(0) species back to Pd(II) so that ring-closure and reformation of the palladacycle can occur.

An alternative Pd(II)/Pd(IV) mechanism was proposed by Jensen for PCP complexes (Scheme 24).[73] The catalytic cycle is initiated by the oxidative addition of a vinyl C–H of $H_2C{=}CHR^2$ to the palladium(II) complexes **72** or **73**. The rate determining reductive elimination of HCl from the Pd(IV) species **74** gives complex **75** and the oxidative addition of R^1Cl generates another Pd(IV) species **76**. Reductive elimination of the coupled product restores the catalyst. The mechanism is unique, invoking successive oxidative addition of both aryl halide and alkene substrates, eliminating the need for the migratory insertion step.

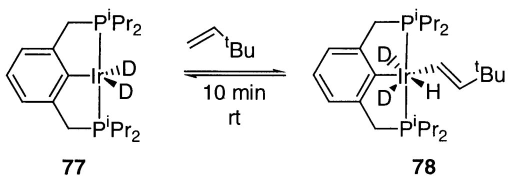
Two literature reports have been quoted in support of the oxidative addition of the alkene to the pincer complex. Previous work by the authors, through NMR studies, showed that vinyl C–H bonds of *tert*-butylethene can be reversibly added to the deuterium labelled iridium complex, $[IrD_2[C_6H_3\text{–}2,6\text{-}(CH_2P^tBu_2)_2]]$ **77**, forming complex **78** (Scheme 25).[75]

The second piece of supporting evidence was found in work by Cotter,[76] where a furyl group was successfully transferred from tributylstannylfuran **80** to form the palladium PCP complex (**82**) and Bu_3SnOTf (**83**) (Scheme 26). Coordination of the furyl compound to complex **79** proceeded reversibly through the tributylstannyl-substituted double bond to give the magnetically inequivalent cationic complexes **81a** and **81b**.

Although the systems quoted above are perfectly valid in



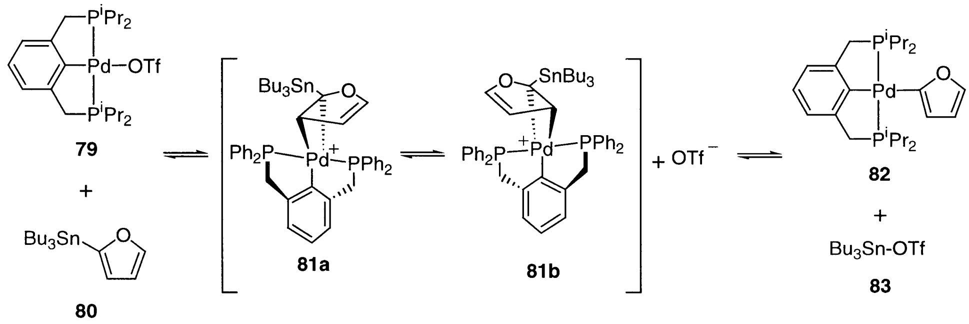
Scheme 24. Jensen's Pd(II)/Pd(IV) mechanism. Q=CH_2 or O; R^1=Ar.



Scheme 25.

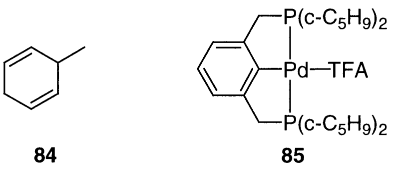
their own right, the reader should exercise caution in drawing parallels between them and complexes **72** and **73**, as they differ quite significantly—the first involves iridium, which is a metal known to undergo C–H activation very readily, and the second is effectively the activation of a carbon–tin bond.

Interestingly, a recent publication has revealed that 1-methyl-1,4-cyclohexadiene **84** significantly inhibits the activity of the PCP pincer catalyst **85** (Scheme 27), which is structurally very similar to Milstein's phosphinato catalyst **69**.[77]



Scheme 26.

The half life of the coupling between bromobenzene and methyl acrylate, with 0.5 mol% of **85** at 135°C, was greatly increased from 4.5 h, when no 1,4-diene was present, to 150 h when 2 equiv. of **84** was added to the reaction. If the mechanism suggested by Jensen operates, then the poisoning effect of the diene could be explained through two vinyl C–H oxidative additions, forming an inactive saturated palladium complex.



Scheme 27.

While the evidence presented for the existence of a Pd(II)/Pd(IV) mechanism is persuasive, detailed mechanistic studies need to be undertaken in order to strengthen the case for its exclusive operation.

3.4. *N*-heterocyclic carbene complexes

N-heterocyclic carbenes (NHC) have a rich and varied chemistry and comprehensive reviews on their synthesis, metal complexes and related chemistry have been published.[78,79]

Palladium complexes of NHC ligands, in particular, have proved to be excellent catalysts not only for the Heck reaction but also for the Suzuki, Stille and Sonagashira reactions.[55,80] The palladium complexes shown in Scheme 28 are those that have been utilised in the Heck reaction. Complexes **86–88** and **91** have been developed by Herrmann,[55,80–83] and **89–90** by Cavell.[84,85]

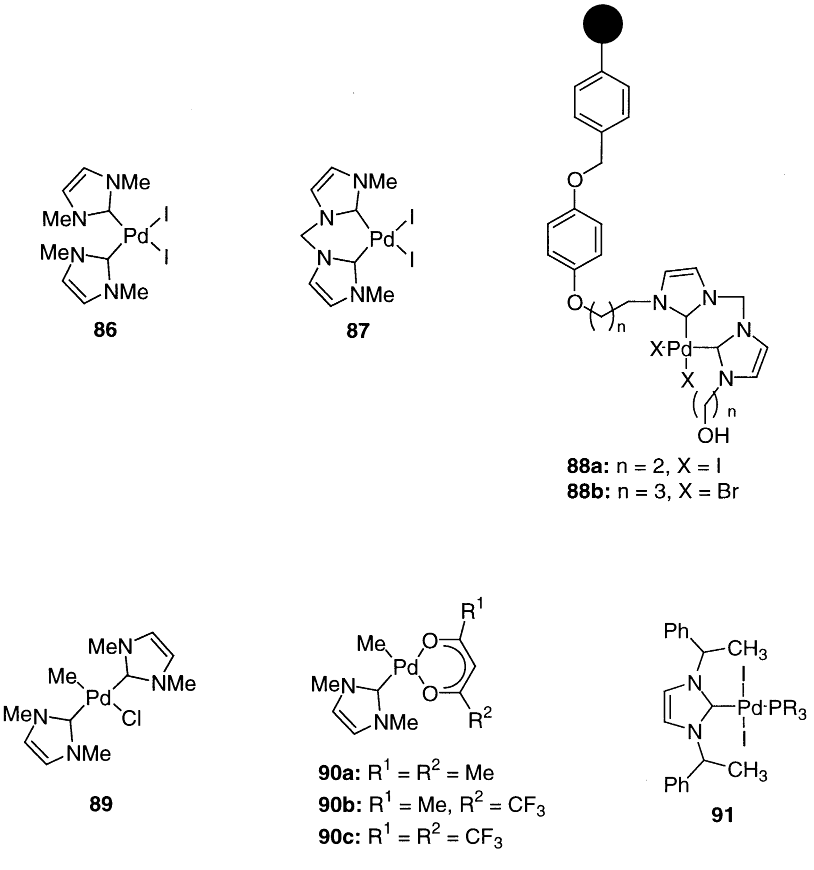
Complexes of this type possess a number of characteristics that contribute to their effectiveness in catalysis and some of their attributes can be favourably compared with the palladacycles described previously. Palladium complexes of NHC are insensitive to air and moisture and are very thermally stable in both the solid state and in solution e.g. **86** decomposes at 305°C and can be boiled in THF under aerobic conditions for several days with no discernible degradation. They become active in catalysis at 80°C and are thus ideal candidates for the activation of challenging aryl chlorides, which require elevated temperatures. They are convenient and cost efficient to prepare and have the potential for modification into polymer-supported reagents (**88**)[83] or mixed carbene–phosphine complexes (**91**).[79,80]

Carbenes are σ-donors where very little, if any, π-back bonding occurs. NHC ligands have been compared to phosphines in that they act as donor ligands, but they differ in one important aspect—carbenes are non-dissociative ligands, the Pd–C bond being very strong and so cleavage is unlikely in solution.[83]

Complexes **86–91** can be divided into two categories. The dihalide complexes **86**, **87** and **91** exhibit an induction period in catalysis, which can be prolonged unless a reducing agent (such as sodium formate, hydrazine or a tetraalkylammonium salt) is added. In contrast, the methylpalladium complexes **89** and **90** do not exhibit an induction period. The polymer-supported catalyst **88** was found to be unaffected by the inclusion of promoters such as Bu_4NBr and PPh_4Cl.

The mechanism proposed for NHC complexes in the Heck reaction is shown in Scheme 29 and has been proposed as proceeding through a cationic Pd(0)/Pd(II) pathway (the use of complexes **86** and **89** is purely illustrative). Experimental evidence presented in support of this route[85] was in agreement with a previously published theoretical study.[86] A Pd(II)/Pd(IV) mechanism was not considered for the carbene complexes.

The catalytic cycle is thought to be initiated through the formation of the Pd(0) species **92**. The Pd(II) dihalide complexes, e.g. complex **86**, are reduced to **92** via a suitable reducing agent. Methylpalladium complexes e.g. complex **89**, have been postulated as being reduced via the oxidative addition of the alkene $H_2C{=}CHR^2$ into the Pd–CH_3 bond, to form complex **93**. β-Hydride elimination affords species **94**, after which base removal of HCl generates the active catalytic species **92**.



86

87

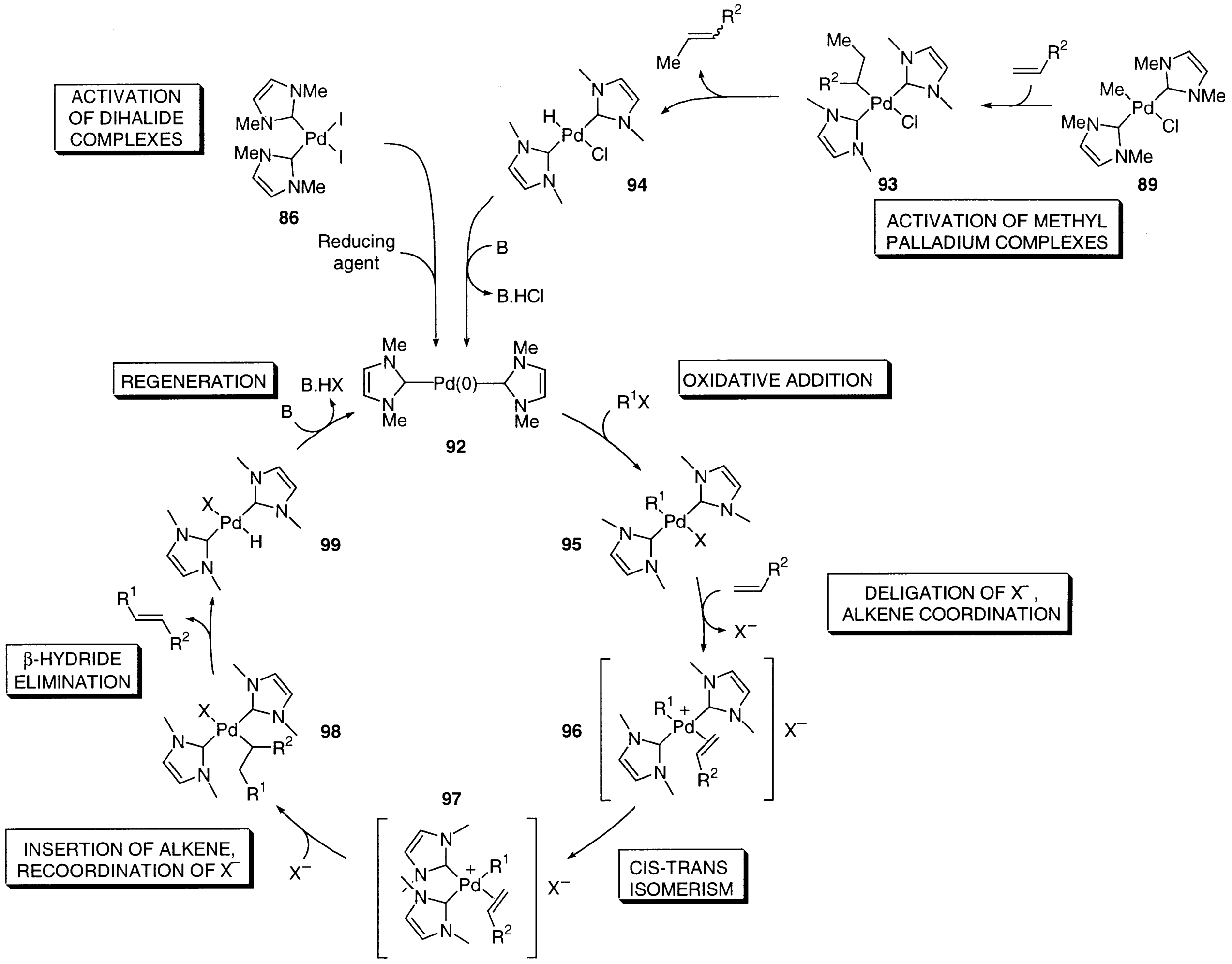
88a: n = 2, X = I
88b: n = 3, X = Br

89

90a: $R^1 = R^2 =$ Me
90b: $R^1 =$ Me, $R^2 = CF_3$
90c: $R^1 = R^2 = CF_3$

91

Scheme 28. NHC complexes employed in the Heck reaction.



Scheme 29. Mechanism of NHC complexes.

The oxidative addition of R^1X to **92** produces the *trans*-$R^1Pd(X)(carbene)_2$ **95**. A free coordination site for insertion of the alkene is created by the deligation of the halide X^- and, in this way, the mechanism switches to a cationic pathway. Loss of a carbene ligand is unlikely due to the strength of the Pd–C bond associated with these ligands. *Cis–trans* isomerism from **96** to **97** allows the insertion of the alkene into the Pd–R^1 bond.

Cationic carbene complexes have been found to be unstable at room temperature.[85] As the temperatures required for catalysis are often elevated, the conversion of **95** to **98** needs to be rapid, giving low concentrations of **96** and **97**, to prevent catalyst degradation taking place. Insertion of the alkene and re-coordination of the halide ion generates the neutral species **98**. β-Hydride elimination gives the new substituted alkene, which is eliminated from the system. Regeneration of the active $Pd(0)(carbene)_2$ species is effected via base removal of HX from **99**.

Three methods of shortening the induction period of NHC complexes in solution phase chemistry are illustrated in Table 14. The first is the addition of a reducing agent to $Pd(carbene)_2X_2$ complexes. Quantitative conversions of activated aryl bromides can be achieved with or without a reducing agent, but the addition of Bu_4NBr led to a significant acceleration of the reaction (entries 1 and 2). The beneficial effect of a reductant can be clearly seen in the reactions of more challenging substrates. On coupling 4-chlorobenzaldehyde with *n*-butyl acrylate, a yield of 12% was obtained in the absence of a reductant, whereas the addition of one equivalent of Bu_4NBr improved the yield to >99% (entries 8 and 9). The same effect can be seen for the reactions of 4-bromobenzene (entries 6 and 7), although in the latter example, the increase in temperature almost certainly had a favourable influence on the outcome.

The second method of avoiding a lengthy induction period is through the in situ generation of a $Pd(0)(carbene)_2$ complex (entry 3). Not only are the initial rates increased, but, additionally, very low concentrations of catalyst can be used, which result in high TONs (>250 000).

The third approach which utilises methylpalladium complexes also leads to a quick and quantitative conversion of the activated 4-bromobenzophenone to the *n*-butyl cinnamate ester (entries 4 and 5).

Interestingly, the dihalide polymer-supported catalysts **88a** and **88b** do not display induction periods, and are not influenced by the addition of a promoter. Excellent conversions can be achieved for activated aryl bromides (entries 10

Table 14. Heck reactions of aryl bromides and chlorides with NHC complexes

Entry	R	X	Catalyst	Mol%	Temp (°C)	Time (h)	Other	Mol%	Yield (%)	Reference
1	COMe	Br	**89**	0.5	125	10	–	–	>99	81
2	COMe	Br	**89**	0.1	130	5	Bu$_4$NBr	20	>99	55
3	COMe	Br	[Pd(0)L]$_2$[a]	4×10^{-4}	125	43	–	–	>99	81
4	COPh	Br	**90a**	0.60	120	<20 min	–	–	100	84
5	COPh	Br	**90b**	0.24	120	25 min	–	–	100	84
6	MeO	Br	**89**	0.67	125	50	–	–	20	81
7	MeO	Br	**89**	0.5	140	12	Bu$_4$NOAc	30	95	55
8	CHO	Cl	**86**	1.0	140	24	–	–	12	81
9	CHO	Cl	**86**	1.0	140	24	Bu$_4$NBr	100	>99	81
10	COMe	Br	**88a**	0.02	150	12	–	–	>99	83
11	COMe	Br	**88b**	0.02	150	60	–	–	>99	83
12	MeO	Br	**88a**	0.02	150	12	–	–	45	83
13	MeO	Br	**88b**	0.02	150	60	–	–	42	83

Conditions: ArX (1 equiv.), *n*-butyl acrylate (1.1–1.4 equiv.), NaOAc (1.1–1.5 equiv.), DMA;

[a] In situ catalyst prepared from Pd(dba)$_2$+**89** (2 equiv.); L=1,3-dimethyldihydroimidazole-2-ylidine.

and 11). The yields obtained for the electron-rich 4-bromoanisole are respectable (entries 12 and 13), especially as relatively low concentrations of catalyst have been used.

Overall, homogeneous NHC complexes show excellent activities for aryl bromides and activated aryl chlorides but deactivated aryl chlorides still remain a challenge. The polymer-supported complexes show good activity for aryl bromides but aryl chlorides could not be induced to react, even under forcing conditions.

3.5. Heterogeneous catalysts

Lin and Finke have proposed a revised definition of heterogeneous catalysts, where they are divided into insoluble, and soluble (e.g. colloidal) systems.[87] In recent years, a number of heterogeneous catalysts have been developed for use in the Heck reaction. The primary drive for their development has been to create a practical alternative to molecular catalysts, which can be difficult and expensive to recover and recycle from the reaction mixture.

An important consideration in developing insoluble heterogeneous catalytic systems for the Heck reaction is the solubility of the B·HX salt.[88] An insoluble salt will smother the surface of the catalyst and the reaction therefore needs to be carried out in a solvent that can solubilise this by-product, removing it from the vicinity of the metal surface.

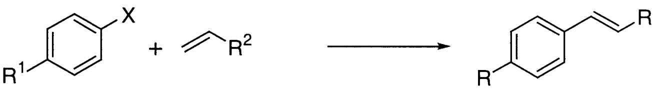
Very little has been published on creating insoluble heterogeneous catalysts suitable for Heck reactions. Kaneda[89] found that Pd–MgO could catalyse the coupling of chlorobenzene and styrene in moderate yield (Table 15; entry 1). Interestingly, the classic hydrogenation catalyst Pd–C was also capable of stilbene formation, although the yield was low (entry 2).

The differences in yield between Pd–MgO and Pd–C could be due to the intrinsic character of the solid support. The basic Mg–O support can donate electrons to the palladium particles creating an electron-rich environment, which is favourable during the oxidative addition of the aryl halide. Pd–C is more acidic and its electron-donating character is therefore minimised.

Pd-TMS11 is formed through vapour deposition of palladium into a mesoporous material. During catalysis, reagents diffuse into the material to react heterogeneously at internal sites.[90,91] Very good conversions were obtained for activated aryl bromides where TONs of 5000 were achieved (Table 15; entry 3). Harsh conditions (170°C, 48 h) were necessary to convert bromobenzene to a cinnamic ester (entry 4). Even at 170°C, however, chlorobenzene remained essentially inactive (entry 5).

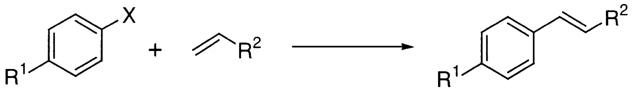
Particles >10 nm in diameter are generally described as colloids and those <10 nm in diameter as clusters.[92] Colloids and clusters differ from insoluble heterogeneous

Table 15. Heck reactions of aryl bromides and chlorides using insoluble heterogeneous catalysts



Entry	R^1	X	R^2	Catalyst	[Pd]	Temp (°C)	Time (h)	Conversion (%)	Reference
1	H	Cl	Ph	Pd–MgO–	0.25 wt%	150	5	42	89
2	H	Cl	Ph	Pd–C	0.50 wt%	150	5	19	89
3	COMe	Br	CO$_2{}^n$Bu	Pd-TMS11	0.02 mol%	120	1	100	90
4	H	Br	CO$_2{}^n$Bu	Pd-TMS11	0.1 mol%	170	48	67	90
5	H	Cl	CO$_2{}^n$Bu	Pd-TMS11	0.1 mol%	170	32	16	90

Table 16. The Heck reactions of aryl bromides and chlorides using Pd sols



Entry	R^1	X	R^2	Preparation of sol	Stabiliser	$[Pd]_{sol}$ (mol%)	Base	Temp (°C)	Time (h)	Conversion (%)	Reference
1	NO_2	Br	Ph	A	Propylene carbonate	3.5	NEt_3	130	5	100	94
2	H	Cl	Ph	A	Propylene carbonate	3.5	Na_2CO_3	155	65	55	94
3	COMe	Br	$CO_2{}^nBu$	B	$(C_8H_{17})_4NBr$	0.05	NaOAc	140	–	97	95
4	COMe	Cl	Ph	B	$(C_8H_{17})_4NBr$	1	NaOAc	140	–	<5	95
5	NO_2	Br	Ph	B	PS-*b*-P4VP	0.05	NBu_3	140	24	92	96
6	Me	Br	Ph	B	PS-*b*-P4VP	0.05	NBu_3	140	72	7	96
7	COMe	Cl	Ph	B	PS-*b*-P4VP	0.05	NBu_3	140	72	0	96

A=Electrochemical reduction; B=Chemical reduction; PS-*b*-P4VP=block copolymer, polystyrene-*b*-poly-4-vinylpyridine.

catalysts in that, while catalysis takes place on the surface of the dispersed metal particles, the colloid or cluster can be soluble. Pd sols are usually prepared either by chemical reduction of a palladium salt or the electrochemical dispersion of palladium metal in the presence of a stabiliser. The stabiliser, e.g. a polymer, tetraalkylammonium salt or surfactant, forms a protective shell around the metal particles, preventing agglomeration and formation of an insoluble precipitate, i.e. palladium black. The sizes of the particles formed depend on the method used, and this in turn influences the activity of the sol. Generally, the smaller the particles, the better the activity, as there are a greater number of surface atoms available for catalysis.[93]

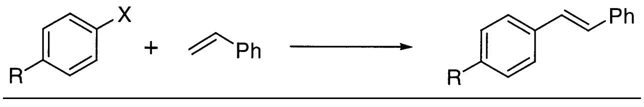
In recent years, considerable effort has been directed towards the synthesis and application of colloids and clusters in the Heck reaction with some degree of success.[93,94] Representative examples of aryl bromides and chlorides that have been successfully transformed are given in Table 16. Excellent conversions can be achieved with activated aryl bromides using the three types of stabilisers shown (entries 1, 3 and 5). The propylene carbonate-stabilized sol can activate chlorobenzene, giving a reasonable conversion of 55% (entry 2), but the block copolymer micelle system and the tetraoctylammonium bromide-stabilised sol cannot convert electron-rich aryl bromides or activated aryl chlorides (entries 4, 6 and 7).

Djakovitch has taken a different approach by encapsulating molecular palladium complexes in zeolites (NaY), where reagents diffuse into the cages, and catalysis occurs homogeneously.[97] As the rate of diffusion is controlled by the internal size of the zeolite, steric hindrance becomes an important contributing factor to the activity of these catalysts. A small catalyst, such as $[Pd(NH_3)_4]^{2+}$, converts 2-bromo-4-fluorobenzene to the substituted stilbene in very high yields at both 100 and 140°C (Table 17; entries 1 and 2), whereas a large sterically hindered palladacycle has very poor activity (entry 3). By using a $[Pd(NH_3)_4]^{2+}$-containing zeolite, 4-bromoanisole can be coupled with styrene in good yield (entry 4). In addition, the activated aryl chloride, 4-chlorobenzophenone, gives reasonable yields without the use of a promoter (entry 5) but the yield increases on addition of tetra-*n*-butylammonium bromide (entry 6). In both examples, a high reaction temperature of 170°C was required.

On comparison, all of the heterogeneous catalysts described here could convert activated aryl bromides in almost quantitative yields. Reasonable conversions can be achieved for bromobenzene using Pd-TMS11, but only the zeolite-based catalyst can convert electron-rich aryl bromides.

Aryl chlorides have again proved to be problematic. The $(C_8H_{17})_4NBr$- and the block copolymer micelle-stabilised colloids failed to catalyse reactions of activated aryl chlorides, whereas the zeolite catalyst gives reasonable yields using Bu_4NBr. Pd–MgO, Pd-TMS11 and the propylene

Table 17. Heck reactions of aryl bromides and chlorides using immobilised catalysts in zeolite NaY



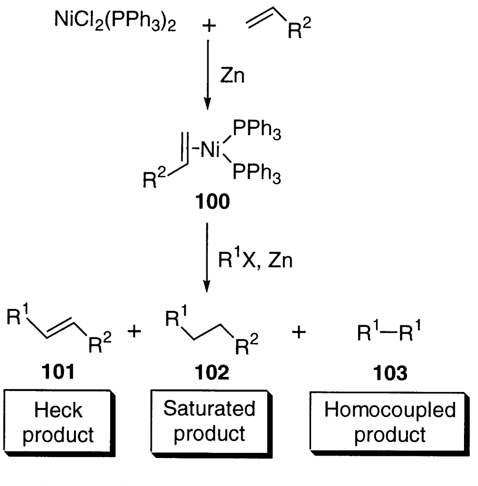
Entry	R	X	Immobilised catalyst	Temp (°C)	Yield (%)[a]
1	F	Br	$[Pd(NH_3)_4]^{2+}$	140	93
2	F	Br	$[Pd(NH_3)_4]^{2+}$	100	95
3	F	Br	Palladacycle[b]	140	3
4	MeO	Br	$[Pd(NH_3)_4]^{2+}$	140	81
5	COPh	Cl	$[Pd(NH_3)_4]^{2+}$	170	44
6	COPh	Cl	$[Pd(NH_3)_4]^{2+c}$	170	59

Conditions: ArX (1 equiv.), styrene (1.5 equiv.), NaOAc (1.5 equiv.), $[Pd]_{zeolite}$ (0.1 mol%), 20 h, DMA.

[a] Yield of *trans* isomer given only.

[b] $Pd[P(o\text{-}Tol)_2(PhCH_2)]^+$.

[c] Bu_4NCl added.



Scheme 30. R^1=aryl; R^2=EWG; X=I, Br, Cl.

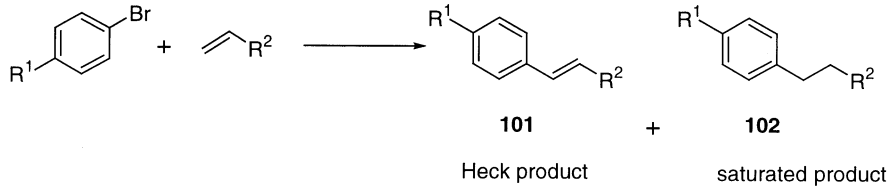
Table 18. Heck reaction of aryl bromides and chlorides catalysed by **100**

Entry	R^1	X	R^2	Time (h)	Yield (%)		
					100	**101**	**102**
1	Ph	Br	Ph	3	25	–	55
2	Ph	Br	CO_2Et	17	3	45	3
3	4-(MeO)C_6H_4	Br	CO_2Et	15	10	20	9
4	Ph	Cl[a]	CO_2Et	40	–	7	2

Conditions: Alkene (1.5 equiv.), $NiCl_2(PPh_3)_2$ (10 mol%), Zn (3 equiv.), THF, then ArX (1 equiv.), 66°C.

[a] Only 20% of PhCl reacted.

Table 19. Heck arylation reaction of aryl bromide with $NiCl_2(PPh_3)_2$/Zn/pyridine



Entry	R^1	R^2	Yield (%)	
			101	**102**
1	H	Ph	86	–
2	MeO	Ph	67	–
3	H	CO_2Me	–	57

Conditions: ArBr (1 equiv.), alkene (2–4 equiv.), $NiCl_2(PPh_3)_2$ (5 mol%), Zn (1 equiv.), pyridine (4 equiv.), 65°C, 4 h.

carbonate-stabilised sol gave satisfactory results for the activation of chlorobenzene. No examples of electron-rich aryl chlorides were given for any of the catalysts.

3.6. Other metals in the Heck reaction

3.6.1. Nickel. Nickel complexes are good candidates for trials as Heck catalysts, as nickel is the first member of the Group 10 triad. In the 1980s, bimetallic systems for executing the Heck reaction were developed. The first utilised $NiCl_2(PPh_3)_2$ in the presence of zinc as a reductant,[98] and while only the *trans*-isomer was obtained for the Heck product, the yields were generally poor, with the formation of saturated and homocoupled by-products (Scheme 30).

The reaction protocol for this example was unusual in that the coordinatively unsaturated (η^2-alkene)bis(triphenylphosphine)nickel(0) complex **100** was first prepared in situ before the addition of the aryl halide. With the exception of the coupling reaction of PhCl, complex 100 was recovered in varying yields from the reaction mixture (Table 18).

The Heck alkene was found to be the major product of the reaction when the recovered yield of **100** was low (Table 18; entries 2 and 3). For the coupling reaction of chlorobenzene with ethyl acrylate, however, only 20% of the aryl halide had reacted (entry 4). When significant amounts of **100** were obtained, the yield of the Heck product (**101**) was often low (entry 1). In all examples, the saturated product **102** was formed, as was the homocoupled derivative **103**, but no information on the extent of formation was given for the latter compound.

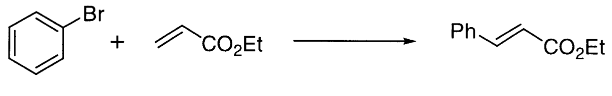
A $NiCl_2(PPh_3)_2$/zinc/pyridine system was also found to be active for the Heck reaction of both activated and deactivated aryl bromides (Table 19; entries 1 and 2).[99]

The reactions of aryl chlorides were unsuccessful, chlorobenzene giving <5% yield on coupling with styrene. Unlike the $NiCl_2(PPh_3)_2$/Zn system, the coupling of bromobenzene and methyl acrylate produced only the saturated product **102** (entry 3). Deuteration experiments concluded that the presence of water was responsible for its formation, and a mechanism involving the Michael addition of $ArNiBr(PPh_3)_2$ to methyl acrylate was presented.[6]

1,3-Diphenylbut-1-ene and biaryl (R^1–R^1) were produced as by-products in the styrene and methyl acrylate experiments, respectively. In both examples, the addition of pyridine suppressed by-product formation. The role of zinc has been assigned as the reducing agent, transforming $NiCl_2(PPh_3)_2$ to Ni(0) and regenerating the active catalytic species from $HNiX(PPh_3)_2$.

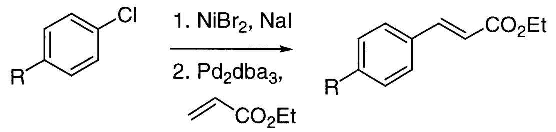
A nickel-catalysed, zinc-free system has been developed by Sugi (Scheme 31).[100] A conversion of 89% was achieved for the reaction between bromobenzene and ethyl acrylate. Good catalytic activity, however, was only achievable at elevated temperatures. This has been attributed to the reduction of the Ni(II) catalyst to Ni(0) via hydrogen transfer from NMP. The traditional Heck pathway was proposed as the mechanism.

Since aryl iodides undergo Heck reactions more readily, Bozell and Vogt developed a method of converting aryl chlorides to the iodide in situ by the addition of sodium iodide.[101] The bimetallic protocol gives very good yields of the cinnamic ester for both electron-rich and



Scheme 31. Conditions: PhBr(1 equiv.), ethyl acrylate (1.25 equiv.), $NiCl_2 \cdot H_2O$ (1 mol%), PPh_3 (2 mol%), Na_2CO_3 (1.25 equiv.), NMP, 160°C, 19 h.

Table 20. Biometallic Pd/Ni protocol for the Heck reaction



Entry	R	Yield
1	MeCO	75
2	H	64
3	MeO	75
4	NO_2	0

Conditions: (1) ArCl (1 equiv.), $NiBr_2$ (20 mol%), NaI (1.1 equiv.), DMF, 140°C, 4–5 h; (2) Alkene (1.1 equiv.), Pd_2dba_3 (0.5 mol%), P(*o*-Tol)$_3$ (0.4 equiv.), Et_3N (1.1 equiv.), DMF, 140°C, 16–18 h.

electron-poor substrates (Table 20; entries 1, 2 and 3). An electron-transfer mechanism was proposed for the chloride/iodide exchange and this is supported by the failure of the reaction in the presence of a radical scavenger such as 4-nitrochlorobenzene (entry 4).

3.6.2. π Complexation of chromium and iron.

The chromium tricarbonyl group [$Cr(CO)_3$] has been equated with a nitro group in terms of its electron-withdrawing ability.[102] The formation of a chromium complex is a well known method of reducing the π-electron density of an arene in order to facilitate previously difficult transformations. Complexation of a chromium tricarbonyl group should, therefore, reduce the C–X bond strength of aryl halides, activating them towards oxidative additive reactions with palladium complexes.[103] Indeed, this idea has been successfully extended to an intramolecular Heck reaction involving electron-rich aryl chlorides (Scheme 32).[104]

This system is particularly attractive in that it can be rendered catalytic in the CTC group, a factor attributed to the lower π-complexing ability of **105** compared to **104**, although the reaction yield is quite low (27%).

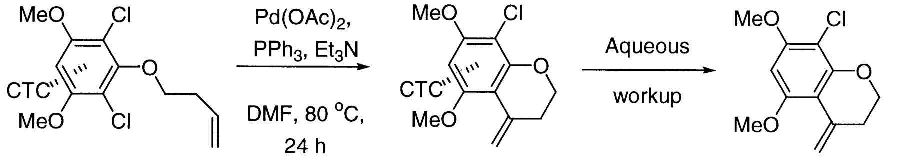
Kündig[105,106] and Scott[107] have applied this methodology successfully to the intramolecular cyclisation of hydroquinolines and the vinylation of methyl vinyl ketone. Palladium-catalysed reactions performed on chromium complexes of aryl chlorides have been reviewed by Mortreux.[103]

The $CpFe^+$ ion is also capable of π-bonding to an arene, and has been compared in terms of π-electron-withdrawing ability to the $Cr(CO)_3$ moiety.[108] On heating **107** with $Pd(PPh_3)_4$, oxidative addition of the palladium complex into the Ar–Cl bond occurred (Scheme 33) where the unusual *cis* orientation was adopted for steric reasons.

Stoichiometric quantities of complex **108** were reacted with styrene and methyl acrylate to give, after decomplexation, stilbene and methyl cinnamate (Scheme 34). As yet, the reaction has not been applied catalytically.

3.6.2.1. Co-catalysts.

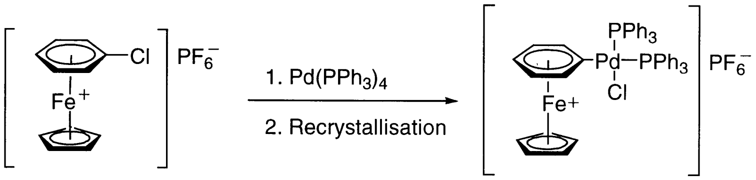
Iyer found that 4-chlorotoluene



104 **105** **106**

Yield 55%

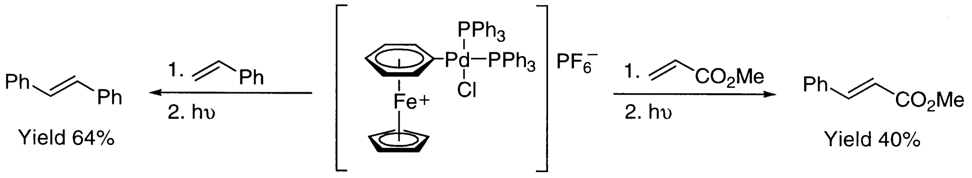
Scheme 32. CTC=chromium tricarbonyl.



107 **108**

Yield 47%

Scheme 33.



108

Scheme 34.

Table 21. Heck reaction with Pd–Cu-exchanged montmorillonite K10 clay

Entry	R^2	Yield
1	CO_2Me	32
2	Ph	51

Conditions: Bromobenzene (1 equiv.), alkene (1–2 equiv.), Pd (0.29 wt%)–Cu (0.36 wt%)-exchanged montmorillonite K10 clay (10 wt%), K_2CO_3 (2.6 equiv.), DMF, reflux, 2 h.

could be activated towards Heck coupling with styrene in the presence of $AlCl_3$ as a cocatalyst, which presumably acts as a Lewis acid.[71] With the cyclopalladated amine complex **67** as catalyst, 4-methylstilbene can be obtained in low yield (4 mol% catalyst, 130°C, 18% yield), whilst addition of tetra-*n*-butylammonium iodide, under the same conditions, gave 28% of the product in 24 h.

Cocatalysts were also employed in heterogeneous catalytic systems. In Pd–Cu-exchanged montmorillonite K10 clay, palladium and copper entities were found to act synergistically during catalysis.[109] The recyclable heterogeneous catalyst can activate aryl iodides and bromides, but aryl chlorides remain as yet unreactive. The yields on coupling bromobenzene with methyl acrylate and styrene are moderate (Table 21, entries 1 and 2). The synergistic interplay between the palladium and copper species, however, makes this system remarkable, i.e. Cu(I)/Cu(II)/Pd(0)/Pd(II).[6] The mechanism is believed to occur via oxidative addition of the aryl halide to copper. Transmetalation to the palladium(II) species then initiates the catalytic cycle via the traditional Heck mechanism.

3.7. Other conditions

3.7.1. Molten salts. The use of molten salts or non-aqueous ionic liquids (NAILs) has been one of the principal pioneering advances to date in Heck chemistry. The application was first reported by Kaufmann[110] and has been significantly developed by Herrmann.[111,112]

Molten salts have a number of advantages over conventional molecular solvents, the first of which being that conventional solvents e.g. DMF and NMP, are not required! Secondly, the volatile components of the reaction are removed by distillation, and so, the entire catalyst-containing melt can therefore be recycled for further use. Finally, as the reagents and products are distilled off, any environmental issues associated with metal leaching can be circumvented.

Many examples of aryl bromide and chloride couplings have been given in the literature[111,112] and the few examples given here are only illustrative of the capabilities of molten salts (Table 22). Activated aryl bromides can be quantitatively converted to the Heck product utilising very low concentrations of catalyst (entry 1). While larger amounts of Herrmann's catalyst are required for activated aryl bromides (entry 2), excellent yields can still be realised.

In considering aryl chlorides, electron-poor substrates can be converted efficiently with low concentrations of catalyst with an appropriate additive. Entry 3 illustrates the formation of a stilbene in 99% yield using Herrmann's catalyst **37** and $AsPh_4Cl$.

While deactivated aryl chlorides are still problematic, very good yields can be achieved on careful choice of the catalytic system. Even though **37** gives disappointing results (entry 4), the application of Fu's catalytic system (Pd_2dba_3/P^tBu_3) gives a respectable 74% yield (entry 5).

The nature of the beneficial effect of ionic liquids in stabilising the active catalytic species is not known. Even if the controversial Pd(II)/Pd(IV) mechanisms are not taken into consideration, the Heck reaction can proceed through a number of pathways, as molten salts are capable of stabilising a wide range of catalytic systems, their stabilising abilities may arise for a variety of reasons. The prevailing opinion for Pd(0)/Pd(II) mechanisms is that the anion effect is in play, creating more stable anionic complexes. Tetraalkylammonium salts are used as stabilisers in colloid formation. Under these conditions, therefore, effective stabilisation of in situ colloids may occur. With respect to the Pd(II)/Pd(IV) mechanism proposed by Shaw,[66] a reversible attack by a nucleophile, e.g. Br^-, AcO^-, is predicted and ionic liquids may facilitate this process.

3.7.2. Phosphine-free conditions. As described in Section 3.1.4, Reetz has developed a method whereby DMG was used to suppress the formation of undesired scrambled

Table 22. The application of molten salts to the Heck reaction

Entry	R^1	X	R^2	Catalyst	[Pd] (mol%)	Additive	[Additive] (mol%)	Molten salt	Temp (°C)	Time (h)	Yield[a] (%)
1	$COCH_3$	Br	Ph	**37**	0.0001	–	–	Bu_4NBr	120	60	100
2	MeO	Br	$CO_2{}^nBu$	**37**	1.0	–	–	$[Bu_4N]OAc$[b]	120	17	>99
3	$COCH_3$	Cl	Ph	**37**	0.1	$AsPh_4Cl$	0.1	Bu_4NBr	150	15	99
4	MeO	Cl	Ph	**37**	4.0	PPh_4Cl	2.0	Bu_4NBr	150	14	18[c]
5	MeO	Cl	Ph	Pd_2dba_3	3.0	P^tBu_3	6.0	Bu_4NBr	150	40	74

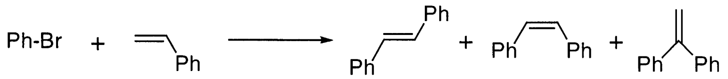
Conditions: ArX (1 equiv.), alkene (1.5 equiv.), NaOAc (1.2 equiv.).

[a] No information on isomer distributions given.

[b] $[Bu_4N]OAc$ was used as both the base and solvent.

[c] Stilbene as major product.

Table 23. Beneficial effect of DMG as an additive in phosphine-free Heck catalysis



Entry	DMG	Conversion (%)	Isomer distribution (%)		
			trans	*cis*	1,1-isomer
1	30 mol%	98	94	1	6
2	–	40	96	1	3

Conditions: PhBr (1 equiv.), styrene (1.5 equiv.), $Pd(CH_3CN)_2Cl_2$ (1.5 mol%), NaOAc (2 equiv.), NMP, 130°C, 10 h.

products.[48] It was subsequently found that a palladium salt, such as $PdCl_2(CH_3CN)_2$ or $Pd(OAc)_2$, is equally effective for the activation of aryl bromides when used in conjunction with DMG. As the reactions were carried out under phosphine-free conditions, the issue of P–C bond cleavage could be avoided.[113]

Table 23 illustrates the beneficial effect of DMG as an additive. A 20:1 ratio of DMG/$Pd(CH_3CN)_2Cl_2$ resulted in a conversion of 98% of bromobenzene compared to 40% for the DMG-free conditions and, in addition, the isomer distribution was marginally improved.

Transmission electron microscopy (TEM) has implicated colloids in these ligand-free systems.[114] Interestingly, this was also found to be true for reactions performed using Jeffrey's phosphine-free conditions where $Pd(OAc)_2$ alone is used with no additives. On investigating ligated systems, i.e. Herrmann's catalyst **37** and [$Pd(OAc)_2$+4 PPh_3] systems, no colloids were detected.

4. Conclusions

The synthetic chemist is today no longer simply limited to the use of aryl iodides in Heck chemistry. Many options are now available for the effective transformations of aryl bromides, and, while great progress has been made in the activation of aryl chlorides, improvements are still necessary. The substrates used in research towards new catalytic systems are, naturally, simple molecules, but the true mark of an efficient new catalytic system is its application to challenging synthetic reactions. Applications in this arena should lead to the emergence of a handful of favoured catalysts.

The Heck reaction has evolved since its introduction, 30 years ago, into a fascinating and sophisticated area of chemistry. A 'one-size-fits-all' mechanism is no longer adequate, and, even though there are still unknown factors at play in Heck mechanisms, it is anticipated that developments in the near future will start to resolve these issues.

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Biographical sketch

Nicole Whitcombe received her BSc degree in Chemistry from Imperial College, London, in 1997. In 2001, she completed her PhD under the direction of Professor Sue Gibson, and Dr Ray McCague of ChiroTech Technology Ltd. Her postgraduate studies involved the synthesis of conformationally constrained amino acids, using the Heck reaction as the key synthetic step. She is currently undertaking post-doctoral research in molecular electronics with Dr Anton Middelberg and Dr Giles Davies at the University of Cambridge, in a collaborative project between the Department of Chemical Engineering and the Cavendish Laboratory.

Mimi Hii was born in 1969 in Malaysia and received her early education in Singapore. She graduated with a BSc(Hons) degree in Chemistry from the University of Leeds, before carrying out postgraduate research work with Professor Bernard Shaw FRS, synthesising novel ligands and their metal complexes. A three-year EPSRC-funded research fellowship ensued with Dr John M. Brown FRS at Oxford University, where she studied the mechanism of the Heck arylation reaction. During this time she was also awarded a Junior Research Fellowship by Wadham College, whilst a Royal Society grant allowed her to carry out collaborative work with Dr Anny Jutand at Ecole Normale Superieure, Paris. The award of a Ramsay Memorial Fellowship (co-sponsored by ICI Strategic Research Fund) allowed her to return to Leeds in 1997, where she initiated independent research before her appointment to a lectureship at King's College London in November 1998. Her research interests are in the field of transition metal-catalysed organic synthesis, especially reactions that lead to the formation of carbon–carbon or carbon–heteroatom bonds.

Sue Gibson, born in 1960, studied Natural Sciences at Cambridge University before undertaking doctoral research work with Professor Stephen Davies at Oxford University. A Research Fellowship awarded by the Royal Society enabled her to study with Professor Albert Eschenmoser at the ETH Zürich, after which she returned to the UK to take up a Lectureship at the University of Warwick in 1985. In 1990 she moved to Imperial College, London, and in 1998, she took up the Daniell Chair of Chemistry at King's College London. Her research interests revolve around the application of transition metals in organic synthesis. Current projects include the use of the Heck reaction to synthesise amino acids embedded in macrocycles, transition metals as linkers in solid-phase chemistry, development of new transition metal catalysts, including immobilised catalysts, the biological and catalytic applications of conformationally constrained amino acids, and the application of chiral base chemistry and tricarbonylchromium(0) complexes of arenes to natural product synthesis and catalyst design