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Coordination Chemistry Reviews 248 (2004) 2283–2321
COORDINATION CHEMISTRY REVIEWS
www.elsevier.com/locate/ccr

The development of palladium catalysts for C–C and C–heteroatom bond forming reactions of aryl chloride substrates

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Received 5 December 2003; accepted 24 June 2004
Available online 25 September 2004

Contents

Abstract

The design and application of new homogeneous palladium catalysts for the formation of C─C and C─heteroatom bonds from aryl chloride substrates is reviewed. Much of the work performed in this area has focused on the synthesis of bulky, electron-rich phosphines and, more recently, carbenes that increase the electron density on the palladium centre(s) sufficiently to facilitate oxidative addition of the strong C─Cl bond. However, there has increasingly been an interest in the development of alternative palladium sources that improve activity when used in association with these ligands, for instance, palladacyclic complexes have played a particular role in this regard.

Keywords: Palladium; Catalyst; Heteroatom; C─C bond forming; Coupling

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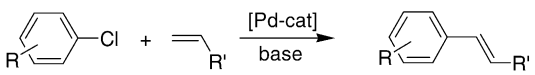
doi:10.1016/j.ccr.2004.06.012

1. Introduction

Palladium catalysed carbon–carbon and carbon–heteroatom bond forming reactions are widely used and powerful tools in organic synthesis [1]. Such processes are typified by the Heck reaction (Scheme 1) and cross-coupling and related reactions where an aryl halide is coupled with a nucleophilic partner. There are many catalyst systems that can be used to catalyse these reactions, although in synthetic laboratories those that are typically employed are either the ubiquitous [$Pd(PPh_3)_4$] or related catalysts formed *in situ* from a triarylphosphine and an appropriate Pd(0) or Pd(II) precursor. In the latter case the palladium is reduced *in situ* to give a Pd(0) active species.

Unfortunately, whilst useful these 'classical' catalyst systems suffer from two major limitations. Generally, they need to be used in high loadings — typically a few mol% Pd and they show little or no activity with aryl chloride substrates. For a reaction to be attractive for application in the industrial sector, such as in the fine chemical or pharmaceutical industries, then palladium contamination of the product must be in the low ppm region, often necessitating expensive product clean-up. This, coupled with the high price of not only the palladium but often the ligands, can make the whole process prohibitively expensive.

Further, the ideal substrates for coupling reactions are aryl chlorides since they tend to be cheaper and more widely available than their bromide or iodide counterparts. Unfortunately the high C–Cl bond strength compared with C–Br and C–I bonds disfavours oxidative addition, the first step in catalytic coupling reactions, making the coupling of such substrates far more challenging [2]. Therefore, there is currently much interest in the synthesis of catalysts that are able to activate aryl chloride substrates at ever lower catalyst loadings. Substantial progress has been made in the last few years, and this review aims to chart the development of the catalyst systems that have emerged and to provide insight into their function, rather than exhaustively list all reported aryl chloride coupling reactions. In particular much of the work performed on heteroaryl chloride substrates indicates that 'classical' catalysts may suffice, therefore they have not been included here to any great extend [3]. The material has been organised primarily by reaction type to allow for some comparisons of catalyst performance in given processes to be made. However, changing conditions such as solvent, base, additives, temperature, time and occasionally — in our experience at least — even the shape of the glassware(!) can have profound effects on activity, therefore comparisons between different systems must be treated with some caution.



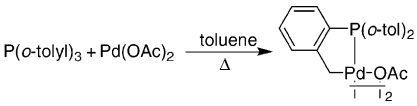
Scheme 1. The Heck coupling of aryl chlorides.

2. Catalysts for the Heck coupling of aryl chlorides

We will look in the first instance at the Heck reaction since, as often occurs [4], this is where a lot of the early attention was focussed. A generic Heck coupling of an aryl chloride substrate is shown in Scheme 1, with the main 1,2-*trans* product shown. In some cases, either or both of the *cis*- or 1,1-isomers may be observed.

2.1. Palladacycles

While the biggest advances in aryl chloride coupling chemistry have occurred within the last five years, in many ways the start of the field proper occurred when Herrmann published the use of palladacyclic catalysts of type 1 in Heck reactions [5]. These catalysts, like many palladacycles, are easily prepared by heating the phosphines with an appropriate palladium(II) source, in this case palladium acetate (Eq. (1)) [6].

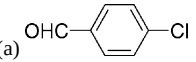
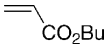
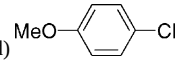
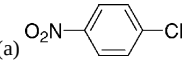
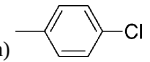
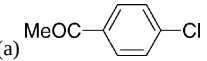
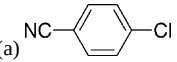
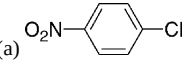
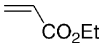
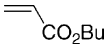
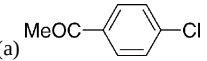
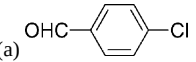
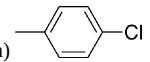
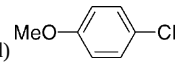


(1)

For the first time turn-over numbers (TONs) of up to 1,000,000 were observed in the Heck coupling of *n*-butylacrylate with the electronically activated (electron-deficient) aryl bromide, 4-bromoacetophenone when **1a** was used as a catalyst [7]. It was later found that this is not a particularly good indication of catalyst performance since TONs of up to 100,000 are observed in coupling reactions with this activated aryl bromide substrate when palladium acetate is employed in the absence of any co-ligands [8]. A better picture of catalyst performance is obtained with deactivated (electron rich) aryl bromides, such as 4-bromoanisole. When this bromide is used then the max TON is substantially lower at 630. More importantly, from the point of view of this review, catalyst **1a** shows some, albeit very limited, activity with aryl chloride substrates, provided that they are electronically activated, such as 4-chloroacetophenone (Table 1 , entry 1). The activity with aryl chloride substrates can be greatly improved by the use of appropriate 'additives' such as tetrabutylammonium bromide (TBAB) or tetraphenylphosphonium chloride (e.g. entries 2 and 3) [9]. The latter phosphonium salt even facilitates the use of the electronically deactivated substrate, 4-chloroanisole, with TONs of up to 190 achieved [10]. The possible roles of the ammonium and phosphonium salt additives will be discussed below.

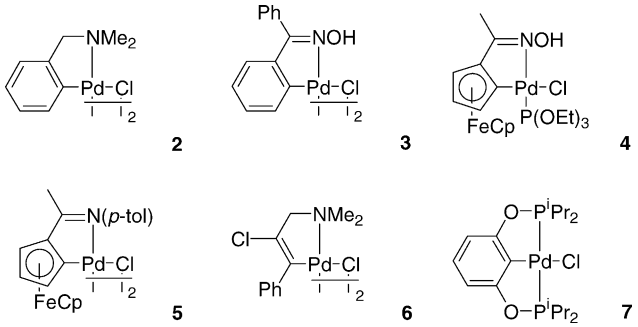
It is not necessary to use a P-donor-based palladacycle, indeed the cyclopalladated amine complex **2**, which had previously been shown to be an active catalyst for the Heck coupling of aryl bromides [11], also shows good activity in the coupling of activated aryl chloride substrates (entry 4) [12]. When the cyclometallated amine ligand is replaced with an oxime, then the catalyst **3** can be used to couple the non-activated substrate 4-chlorotoluene provided again that an ammonium salt is added to facilitate the reaction (entry

Table 1
Selected Heck coupling reactions with aryl chloride substrates catalysed by palladacyclic complexes

Entry	Catalyst	Catalyst loading (mol% Pd)	Aryl chloride (a, n, d)[a]	Alkene	Solvent[b]/base	Temperature (°C)	Time (h)	Conversion[c] {isolated yield} (%)	Reference
1	**1a**	1	(a) 		DMA/NaOAc	140	24	12	[5]
2	**1a** + $[NBu_4]Br$ (100 eq.)	0.2	”	”	DMA/NaOAc	130	24	81	[9]
3	**1a** + $[PPh_4]Cl$ (5 eq.)	0.2	(d) 		DMA/NaOAc	150	60	38	[10]
4	**2**	0.01	(a) 	”	NMP/K_2CO_3	150	42	71	[12]
5	**3** + $[NBu_4]I$	Not specified	(n) 	”	”	130	24	28	[12]
6	**4** + $[NBu_4]Br$	Not specified	(a) 	”	NMP/NaOAc	140–150	Not specified	53	[13]
7	”	”	(a) 	”	”	”	”	37	[13]
8	**5** + $[NBu_4]Br$ (*ca.* 500 eq.)	0.18	(a) 		DMF/Et_3N	140	10	{73}	[14]
9	**6** + $[NBu_4]Br$ (20 eq.)	1.0	”		DMA/NaOAc	150	24	100	[15]
10	**7**	0.67	(a) 		Dioxane/CsOAc	120	120	>99	[16]
11	”	”	(a) 	”	”	”	”	82	[16]
12	”	”	(n) 	”	”	”	”	85	[16]
13	”	”	(d) 	”	”	”	”	88	[16]

[a] a: activated, n: non-activated, d: deactivated (with respect to oxidative addition).
[b] DMA: *N*,*N*-dimethylacetamide, DMF: *N*,*N*-dimethylformamide, NMP: *N*-methylpyrolidone.
[c] Conversion to Heck products, all isomers.

5). Iyer showed that a phosphite adduct of a cyclometallated ferrocenyloxime, complex **4**, can be used in the coupling of activated aryl chlorides (entries 6 and 7) [13]. Similarly, the orthopalladated ferrocenylimine complex **5** can be used for an activated chloride in the presence of TBAB (entry 8) [14]. It is not necessary to have an aromatic ring as part of the cyclometallated ligand — recently Dupont and co-workers showed that the chloropalladated propargyl amine complex **6** can also be used with activated aryl chlorides (e.g. entry 9) [15].

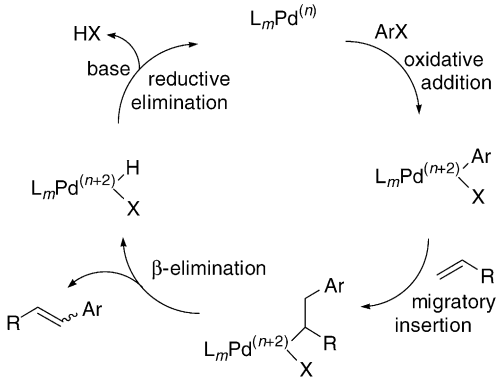


2 **3** **4** **5** **6** **7**

While non-phosphorus-containing palladacycles can be used with activated aryl chlorides, by far the best activity reported to date in the Heck reaction catalysed by a palladacycle is with the bis(diisopropylphosphinite) pincer complex **7** [16]. A brief solvent/base optimisation study revealed that CsOAc in 1,4-dioxane allows the facile coupling not only of activated and non-activated but also deactivated aryl chloride substrates (entries 10–13). At 120 °C, the reactions are sluggish and require a reaction time of 5 days, however heating to 180 °C leads to good isolated yields within 24 h.

The use of catalysts of type **1** in Heck coupling reactions started an interesting debate in the field — does catalysis occur *via* a classical Pd(0)/Pd(II) pathway after reduction of the precatalyst (Scheme 2, $n = 0$) or rather does it proceed via a Pd(II)/Pd(IV) manifold ($n = +2$)?

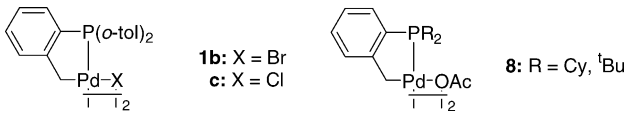
Herrmann originally argued that the lack of visible palladium black deposition when complexes of the type **1** are used as catalysts and the fact that it is possible to isolate high yields of the palladacycle **1** in which the only change is that the dimer is bridged by the halide from the substrate, indicate



Scheme 2. Highly simplified mechanism for the Heck reaction.

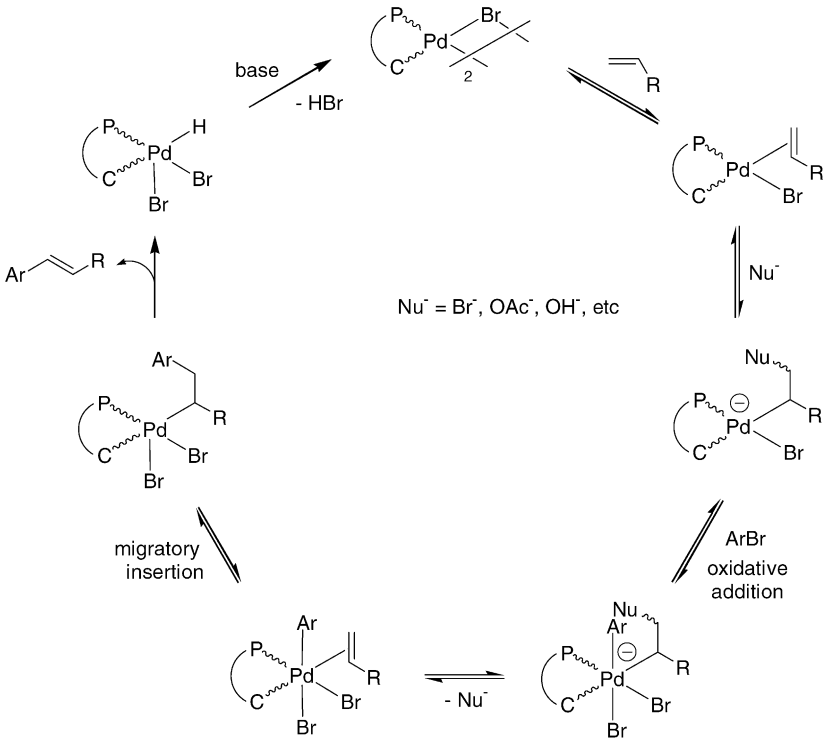
that maybe Pd(0) is not being formed [6d]. Following the coupling of 4-bromobenzaldehyde with *n*-butyl acrylate catalysed by **1a** by ^{31}P NMR spectroscopy gave no evidence for the formation of zerovalent palladium–phosphine complexes. The only complexes observed were palladacycles with bromide co-ligands and mononuclear 'ate' complexes formed by the reaction of dimers with anions present in the reaction [5]. Taken together, this data implied that a Pd(II)/Pd(IV) pathway may be operative. Such a pathway was proposed by Shaw and invokes the reversible attack of a nucleophile present in the reaction (e.g. acetate, halide) on a coordinated alkene to generate a σ-alkyl complex which is sufficiently electron-rich to promote the oxidative addition of the aryl halide to the Pd(II) center [17]. This mechanism is outlined in Scheme 3 for an aryl bromide substrate with a generic phospha-palladacycle. However, as yet, there is essentially no firm evidence that such a pathway is operative.

Oxidative addition of aryl halides to complexes such as **1** is not observed [6d], suggesting a simple mechanism such as that shown in Scheme 3 with $n = 2$ is not plausible. Heating complexes of the type **1** with alkenes leads to the formation of palladium black, indicative of a reductive process, but there is no evidence for insertion into the Pd–C bond. Therefore, Herrmann speculated that simple thermal decomposition of the complexes **1** may lead to the true active catalysts. Indeed, the order of activity of the palladacycles **1** with varying anions is **1a** > **1b** (X = Br) > **1c** (X = Cl) [6d], which is the opposite trend for the thermal stability of Pd(II) salts with these anions [18]. The alkyl substituted palladacycles **8** are more electron-rich than the complex **1a**, therefore if a Pd(II)/Pd(IV) pathway is operative they should show higher activity. In practice, they are poorer catalysts [19]. Conversely, alkyl-substituted complexes such as **8** are more thermally stable than the complex **1a** which further supports the suggestion that the true catalysts are formed by a thermal reduction process.



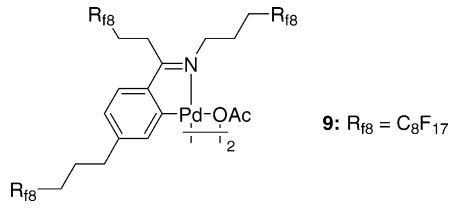
Beletskaya et al. proposed a zerovalent active catalyst in Heck coupling reactions when N-based palladacycles are used as catalysts [20]. The mechanism of liberation of the active catalysts that they proposed is outlined in Scheme 4. Essentially, the palladacycle undergoes a ring-opening process which can be described as a non-catalytic Heck reaction. While this is plausible, Nowotny et al. had previously demonstrated that reduction of a polystyrene-immobilised imine-based palladacycle can occur under thermal conditions, even in the absence of the Heck reaction components [21].

One thing that is apparent from Table 1 is that, with the exception of complex **7**, it always seems necessary to include an 'additive' — typically an ammonium or phosphonium salt — to the palladacyclic precatalyst in order to get optimum, or indeed any, activity with aryl chloride substrates. Given

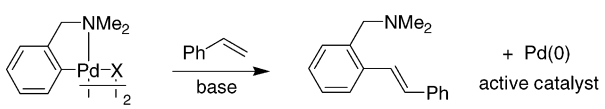


Scheme 3. A putative mechanism for the Heck coupling of aryl bromides catalysed by palladacycles.

that it is now generally accepted that the true active catalysts are zerovalent species formed by reduction of the Pd(II) palladacyclic precatalysts, it seems likely that the main role of the additives is to stabilise catalytically active colloidal or nanoparticulate palladium. Indeed, aliquots taken from a Heck reaction catalysed by the fluorous ponytail-modified imine palladacycle **9** and analysed by TEM show the presence of palladium nanoparticles [22]. Colloidal palladium systems supported by TBAB/water mixtures have recently been shown to catalyse aryl chloride coupling reactions [23]. Therefore, it seems likely that in the case of most, if not all of the complexes **1**–**6**, the main function of the palladacycle is to deliver a zerovalent active catalyst species at such a rate and in such a manner as to retard decomposition to bulk metal.

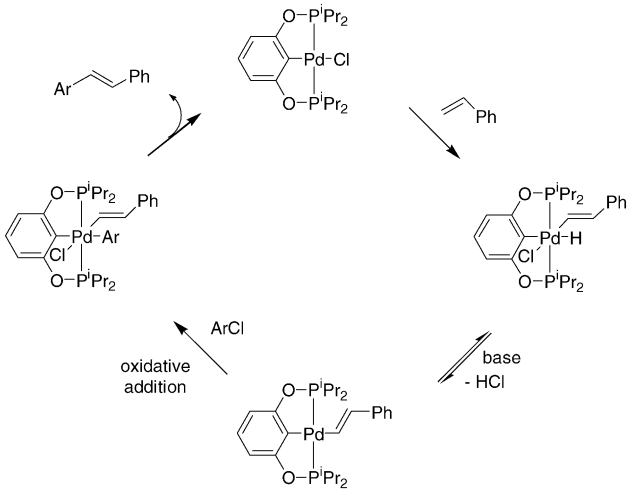


In contrast with the other catalyst systems presented in Table 1, the PCP-pincer complex **7** does not require the use of additives to show good activity, even with electronically deactivated aryl chlorides. This may imply that here the active catalyst is not colloidal palladium but rather is a well defined molecular species, and currently it is not possible to rule out a Pd(II)/Pd(IV) catalytic manifold [16]. Jensen proposed a catalytic cycle that proceeds via the C–H activation of the olefin at a Pd(II) centre(s) followed by oxidative addition (Scheme 5).



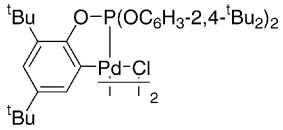
Scheme 4. Putative Heck-type ring opening of a palladacycle.

Palladacycles have been used in the Heck coupling of aryl chlorides in non-conventional solvents. Thus, Herrmann and co-workers showed that the palladacyclic complexes **1a** and **10**, amongst other palladium precatalysts, can be used in the



Scheme 5. Proposed mechanism for Heck coupling catalysed by complex **7**.

Heck coupling of chlorobenzene with styrene in non-aqueous ionic liquids [24].



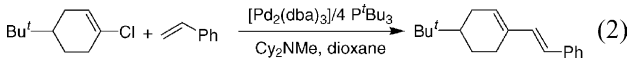
10

Currently, palladacyclic complexes, despite being amongst the first catalysts to show real promise in the Heck coupling of aryl chloride substrates, are still some way from being routinely usable in such reactions. As we will see later, that is not true for other coupling reactions, where palladacycles can show unsurpassed activity.

2.2. Phosphines

Simple phosphine complexes of palladium have been used to varying effect in the Heck coupling of aryl chloride substrates. Pioneering work was performed a decade ago by Milstein and co-workers, using electron-rich chelating bis-phosphine complexes [25–27]. They found that the chelating ligand 1,4-bis(diisopropylphosphino)butane could be used not only for the coupling of activated (e.g. Table 2, entry 1) and non-activated aryl chlorides but even showed some activity with the deactivated substrate 4-chloroanisole (entry 2). By contrast the smaller chelate ring forming ligand 1,3-bis(diisopropylphosphino)propane shows essentially no activity in the coupling of the non-activated substrate chlorobenzene (entry 3). Interestingly, the problem here cannot be the oxidative addition of the aryl chloride as this catalyst system shows activity in the carbonylative couplings of aryl chlorides [28]. The greater activity of the dippb-containing catalysts compared with the dippp analogue in the Heck reaction is rationalised in terms of the greater ability of the larger ring-sized chelate to undergo mono-phosphine dissociation, allowing the generation of *trans* phosphine complexes [27]. Remarkably, when the reaction is repeated without base but in the presence of zinc, then a good conversion to stilbene results (entry 4) [26]. This base-free modification even leads to better activity with the deactivated substrate 4-chloroanisole. The role of the zinc is to reduce a palladium dichloride adduct formed during the catalytic reaction [26,27].

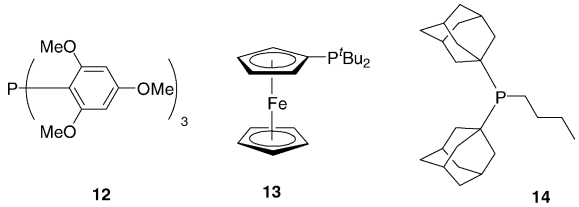
The diisopropyl substituents on the chelating trialkylphosphine ligands described above render them both comparatively large and electron rich. The high σ-basicity of the phosphine gives electron-rich Pd(0) complexes which are able to oxidatively add electron-rich aryl chlorides. In an extension of this idea Littke and Fu examined the possibility of using the very large and electron-rich phosphine tri-*tert*-butylphosphine as a ligand in the Heck coupling of aryl chlorides [29,30]. They found that $[Pd_2(dba)_3]/P^tBu_3$ mixtures give good activity in the coupling of activated, non-activated and deactivated chlorides when Cs_2CO_3 is used as a base in 1,4-dioxane (e.g. entries 6–8) [29]. They later found that when the Cs_2CO_3 is replaced with the tertiary amine Cy_2NMe then activated aryl chloride substrates can even be coupled at room temperature (e.g. entries 9–11) with a range of mono- and di-substituted olefins. Increasing the temperature facilitates the coupling of non-activated, deactivated and sterically hindered aryl chlorides, even at comparatively low Pd loadings (e.g. entries 12–14). This activity is not limited to aryl chloride substrates; deactivated vinyl chlorides can also be used (Eq. (2)). The activity of the complex prepared *in situ* from $[Pd_2(dba)_3]$ and P^tBu_3 is almost identical to that of the preformed bis-phosphine complex $[Pd(P^tBu_3)_2]$, **11**, (compare entries 14 and 15), the advantage of the preformed systems is that it is air-stable making it much easier to handle than the free phosphine, it is also commercially available. In order to address the problem of the high air-sensitivity of the free phosphine, Netherton and Fu examined the possibility of using a phosphonium salt of P^tBu_3 as an air-stable precursor which can liberate the free phosphine *in situ* by deprotonation with the base required for the Heck coupling [31]. Thus, when the phosphine is replaced by $[HP^tBu_3][BF_4]$ then similar, or better performances are seen.



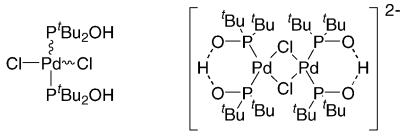
(2)

It seems likely that the true active catalyst when tri-*tert*-butylphosphine systems are used is a mono-phosphine species since increasing the ratio of P:Pd from 1:1 to 2:1 in the room temperature coupling of aryl chlorides is deleterious to the rate [30]. Kinetic studies indicate that the rate-determining step is oxidative addition of the aryl chloride.

As mentioned above, the use of highly σ-basic phosphines renders the palladium centre(s) electron-rich and should therefore facilitate oxidative addition. However, more subtle factors must come into play. For instance Littke and Fu demonstrated that the palladium complexes of the triarylphosphine **12** show essentially no activity in the coupling of chlorobenzene with methylacrylate, despite the fact that this phosphine has very similar electronic and steric properties to P^tBu_3 [29].



12 **13** **14**



15 **16**

As part of his study into the use of non-aqueous ionic liquids as solvents for the Heck coupling of chlorobenzene with styrene, Herrmann found that a Pd/P^tBu_3 system gave the best results in molten TBAB [24]. Hartwig also uncovered

Table 2
Selected Heck coupling reactions with aryl chloride substrates catalysed by simple phosphine complexes

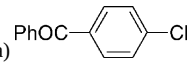
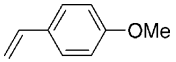
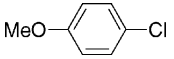
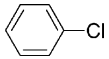
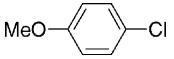
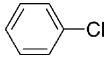
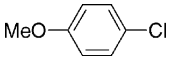
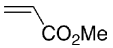
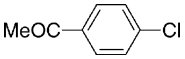
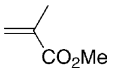
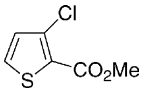
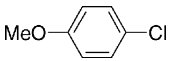
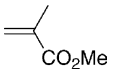
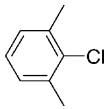
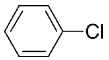
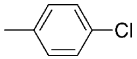
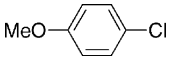
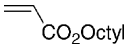
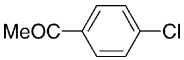
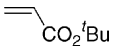
Entry	Catalyst	Catalyst loading (mol% Pd)	Aryl chloride (a, n, d)[a]	Alkene	Solvent[b]/base	Temperature (°C)	Time (h)	Conversion[c] {isolated yield} (%)	Reference
1	$Pd(OAc)_2$ + 2dippb[d]	1.0	(a) 		DMF/NaOAc	150	24	100	[25]
2	”	”	(d) 		”	”	”	21	[25]
3	$Pd(OAc)_2$ + 2dippp[d]	”	(n) 	”	”	”	”	3	[25]
4	”	”	”	”	DMF base free-Zn (0.5 eq. per PhCl) used as an additive	140	24	88	[26]
5	”	”	(d) 	”	”	”	”	49	[26]
6	$[Pd_2(dba)_3]$ + 4 P^tBu_3	1.5	(n) 	”	Cs_2CO_3/dioxane	120	21	{83}	[29]
7	”	”	(d) 	”	”	”	30	{84}	[29]
8	”	”	”		”	”	24	{82}	[29]
9	$[Pd_2(dba)_3]$ + 2 P^tBu_3	1.5	(a) 		Cy_2NMe/dioxane	r.t.	32	{78}	[30]
10	”	”	”		”	”	36	{79}	[30]
11	”	”	(a) 		”	”	23	{87}	[30]
12	$[Pd_2(dba)_3]$ + 4 P^tBu_3	1.5	(d) 		”	120	53	{72}	[30]

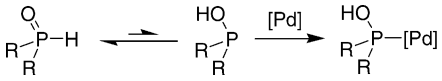
Table 2 (*Continued*)

Entry	Catalyst	Catalyst loading (mol% Pd)	Aryl chloride (a, n, d)[a]	Alkene	Solvent[b]/base	Temperature (°C)	Time (h)	Conversion[c] {isolated yield} (%)	Reference
13	”	”		”	”	”	39	{80}	[30]
14	$[Pd_2(dba)_3]$ + 2 P^tBu_3	0.2	(n) 	”	”	”	48	{67}	[30]
15	$[Pd(P^tBu_3)_2]$, **11**	”	”	”	”	”	”	{63}	[30]
16	$[Pd(dba)_2]$ + 2 **14**	1.0	(n) 		K_3PO_4/dioxane	120	24	{98}	[33]
17	”	2.0	(d) 		”	”	”	{82}	[33]
18	**15**	3.0	(a) 		NaOAc/DMF	135	5–24	{66}	[34]
19	**16**	3.0	”	”	K_2CO_3/DMF	135	5–24	{77}	[34]

[a] a: activated, n: non-activated, d: deactivated (with respect to oxidative addition).
[b] DMF: *N*,*N*-dimethylformamide.
[c] To Heck products, all isomers.
[d] dippb: 1,4-bis(diisopropylphosphino)butane, dippp: 1,3-bis(diisopropylphosphino)propane.

the utility of this phosphine in the Heck coupling of aryl chlorides using a fluorescence-based assay technique [32]. This high-throughput screening method revealed that even better results are obtained in the coupling of 4-chloroanisole with butylacrylate if the P^tBu_3 is replaced with the ferrocenyl-containing analogue 13. Examining the coupling of 4-chlorotoluene with styrene catalysed by complexes formed *in situ* with a range of phosphines, Beller and co-workers showed that very high yields of coupled product are obtained when diadamantylbutylphosphine, **14**, is used [33]. This system can be used for a range of couplings of non-activated and deactivated aryl chlorides (e.g. entries 16 and 17) and again shows higher activity than P^tBu_3 in comparable reactions.

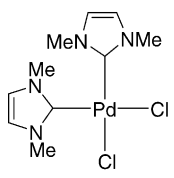
Secondary dialkyl phosphine oxides exist in equilibrium with hydroxyphosphines, (Eq. (3)) which, when coordinated to palladium, give complexes that are able to catalyse the Heck coupling of activated aryl chlorides [34]. Both the neutral complex **15** and the dianion 16 act as catalysts for the coupling of the activated substrate 4-chloroacetophenone with *tert*-butylacrylate (Table 2, entries 18 and 19).



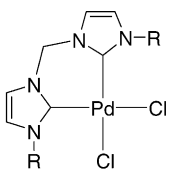
(3)

2.3. Carbenes

N-Heterocyclic carbenes derived from imidazolium salts and related carbene ligands are strong σ-donors and very weak π-acids which tend to form strongly coordinated complexes with Pd(II). The high basicity and low lability may make them ideal ligands for aryl chloride activation since they will produce electron rich centers capable of oxidatively adding such substrates [35]. Herrmann and co-workers performed the early work in this field and demonstrated that the bis-carbene complex **17** could be used to couple activated aryl chlorides, particularly when $[NBu_4]Br$ is used as an additive (e.g. Table 3, entries 1 and 2) [36]. The chelating bis-carbene complexes **18** have also been shown to be active with activated aryl chlorides (entries 3 and 4), although no activity is seen with **18b** with non-activated substrate chlorobenzene (entry 5) [37,38]. In these cases, it is likely that the true active catalyst is a zerovalent palladium complex of the form PdL_n (L = carbene) produced by *in situ* reduction of the palladium(II) precatalyst. Indeed, complexes formed *in situ* between $[Pd(dba)_2]$ and the free carbene ligands do not suffer from the protracted induction time observed with the complex **17** [36].

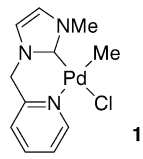


17

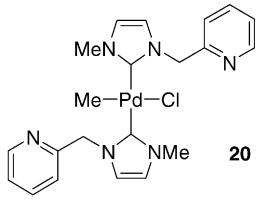


18a: R = Me
b: R = CH_2CH_2OH

Carbene ligands with *N*-heterocyclic pendant donors have also been used with some success in the Heck coupling of aryl chloride substrates. McGuiness and Cavell showed that the pyridyl-carbene containing complexes **19** and **20** can couple butylacrylate with 4-chlorobenzaldehyde (entries 6 and 7), [39] while Gade and co-workers demonstrated the utility of the oxazolinyl-carbene-containing complex **21** with activated aryl chlorides (e.g. entry 8) [40]. Similarly, Crabtree and co-workers demonstrated the use of the bis-carbene CNC-pincer complex **22** (entry 9) [41]. In these cases, the addition of a quaternary ammonium salt is necessary.



19



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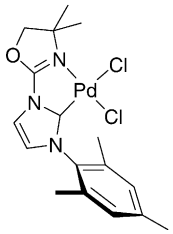
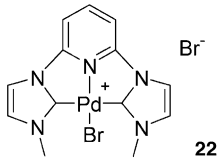
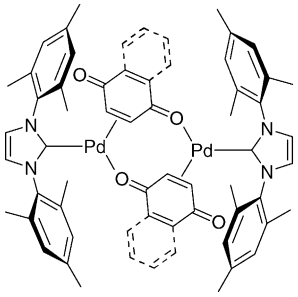


21



22

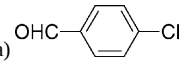
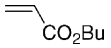
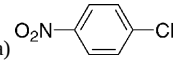
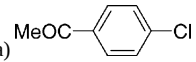
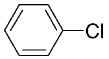
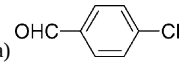
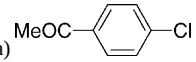
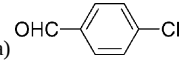
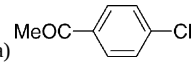
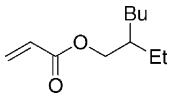
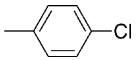
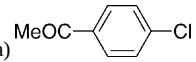
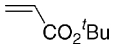
Beller and co-workers showed that such salts could be used neat as a solvent for the coupling of activated and non-activated chlorides using the zerovalent monocarbene complexes **23** (e.g. entries 10 and 11) [42].



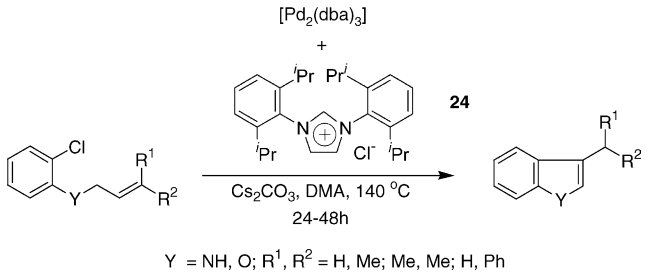
23a: bridging ligand = naphthoquinone
b: bridging ligand = benzoquinone

It is not necessary to pre-form palladium carbene complexes, catalysts can be formed *in situ* from an appropriate palladium precursor and an imidazolium salt; the deprotonation is mediated by the base used in the coupling reaction. Kofie and Caddick have recently exploited this for the synthesis of benzofurans and indoles via intramolecular Heck couplings of aryl chlorides using the bulky imidazolium salt **24** as a carbene precursor (Scheme 6) [43]. Again the best results are obtained when TBAB is added to the reaction. Meanwhile Zhang and co-workers have used the tetraimidazolium salt **25** in the coupling of 4-chloroacetophenone with *tert*-butylacrylate (Table 3, entry 12) [44].

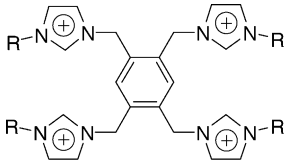
Table 3
Selected Heck coupling reactions with aryl chloride substrates catalysed by heterocyclic carbene complexes

Entry	Catalyst	Catalyst loading (mol% Pd)	Aryl chloride (a, n, d)[a]	Alkene	Solvent[b]/base	Temperature (°C)	Time (h)	Conversion[c] {isolated yield} (%)	Reference
1	**17**	1.0	(a) 		DMA/NaOAc	140	24	12	[36]
2	**17** + $[NBu_4]Br$ (100 eq.)	”	”	”	”	”	”	99	[36]
3	**18b** + $[NBu_4]Br$ (200 eq.)	1.0	(a) 	”	”	150	72	99	[37]
4	”	”	(a) 	”	”	150	19	59	[37]
5	”	”	(n) 	”	”	160	30	0	[37]
6	**19** + $[NPr_4]Br$ (200 eq.)	0.21	(a) 	”	”	120	24	75	[39]
7	**20** + $[NPr_4]Br$ (200 eq.)	0.2	”	”	”	”	”	66	[39]
8	**21** + $[NBu_4]Br$ (100 eq.)	0.2	(a) 		DMA/K_3PO_4	135	18	100	[40]
9	**22** + $[NBu_4]Br$ (4 eq.)	5.0	(a) 	”	DMA/NaOAc	Reflux	20	75	[41]
10	**23a**	0.4	(a) 		Molten $[NBu_4]Br$/NaOAc	140	24	100	[42]
11	”	2.0	(n) 	”	”	”	48	48	[42]
12	$Pd(OAc)_2$ + 0.525	1.0	(a) 		NMP/K_2CO_3	120	24	{57}	[44]

[a] a: activated, n: non-activated, d: deactivated (with respect to oxidative addition).
[b] DMA: *N*,*N*-dimethylacetamide, NMP: *N*-methylpyrolidone.
[c] To Heck products, all isomers.



Scheme 6.

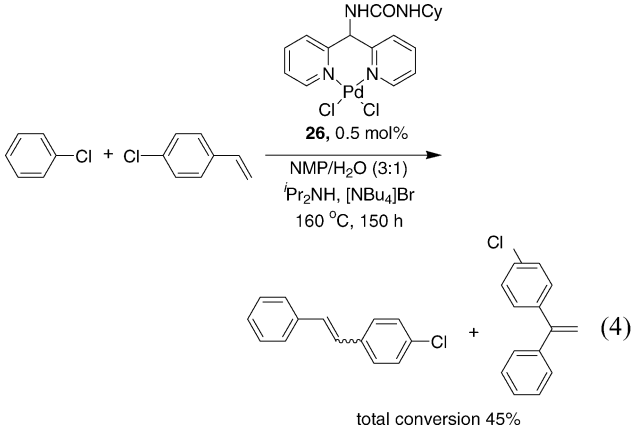


25: R = 2,6-diisopropylphenyl

In general, it can be seen that while carbene ligands are able to facilitate the Heck coupling of aryl chlorides, to date the reactions are essentially limited to activated and non-activated substrates. Even then optimal activity is only seen when an ammonium salt additive is used. While these systems hold promise they are still lagging behind phosphine complexes in their overall utility in this class of reaction.

2.4. Miscellaneous catalysts

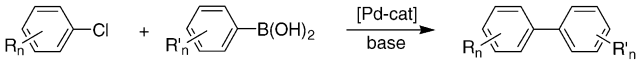
Nájera and co-workers recently demonstrated the use of the bis-pyridyl complex **26** in the coupling of chlorobenzene with 4-chlorostyrene (Eq. (4)). Again tetrabutylammonium bromide is necessary, suggesting that the active catalyst may be colloidal palladium [45].



(4)

3. The Suzuki coupling of aryl chlorides

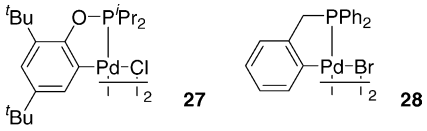
The Suzuki reaction is an extremely powerful method for the formation of biaryl compounds [46], consequently there has been considerable attention focussed on the development of catalysts that are able to promote the coupling of aryl chloride substrates (Scheme 7).



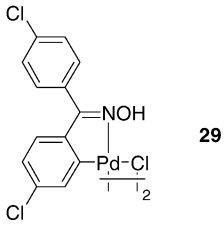
Scheme 7. The Suzuki coupling of aryl chlorides.

3.1. Palladacycles

As with the Heck reaction, the initial studies on the use of palladacyclic catalysts in the Suzuki coupling of aryl chlorides focussed on the use of the complex **1a**. Thus Beller et al. found that reasonable levels of activity result in the coupling of phenylboronic acid with the activated substrate 4-chloroacetophenone (Table 4, entry 1) [47]. We showed that the somewhat more electron deficient phosphinite-based palladacycle **27**, while showing only very limited activity with deactivated substrates (entries 2 and 3) [48], can be used to good effect in the coupling of activated and non-activated aryl chlorides (e.g. entries 4 and 5) [49]. By contrast, the related, orthopalladated benzylphosphine complex **28**, reported by Gibson and Cole-Hamilton, shows no activity with 4-chloroacetophenone and only limited activity with 4-chlorobenzaldehyde [50]. In this case, the product is contaminated by substantial amounts of 1-(4-chlorophenyl)-1-phenylmethanol and 1,4-biphenyl-1-phenylmethanol.



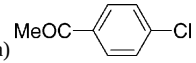
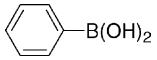
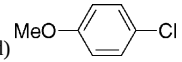
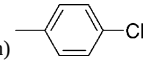
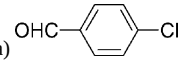
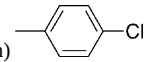
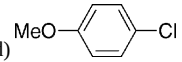
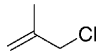
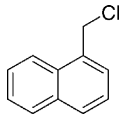
27 **28**



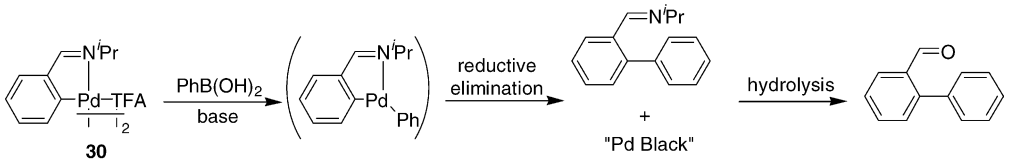
29

Activity is not limited to phosphorus-based palladacycles; Nájera and co-workers found that the oxime-derived palladacycle **29** can be used to couple not only activated and non-activated aryl chlorides (e.g. entry 6), but that they can also be used with deactivated substrates such as 4-chloroanisole (entry 7) [51]. Further, this catalyst can be used to couple allylic and benzylic chlorides (entries 8 and 9). Related catalysts display varying degrees of success in the Suzuki coupling of chloride substrates in water under air [52]. Again, it is necessary in all cases to use TBAB as an additive. We have recently found that simple colloidal palladium catalysts derived from palladium acetate in a TBAB–water mixture are effective catalysts for the Suzuki coupling of activated to deactivated aryl chlorides [23a]. In addition, we have shown that imine based-palladacycles such as **30** undergo a reductive ring-opening reaction in the presence of arylboronic acids and a base (Scheme 8) [53], therefore it seems highly likely that the true active catalyst derived from oxime-base palladacycles is in fact colloidal palladium supported by the TBAB.

Table 4
Selected Suzuki coupling reactions with chloride substrates catalysed by palladacyclic complexes

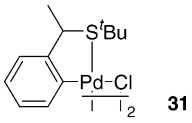
Entry	Catalyst	Catalyst loading (mol% Pd)	Chloride substrate (a, n, d)[a]	Aryl boronic acid	Solvent[b]/base	Temperature (°C)	Time (h)	Conversion {isolated yield} (%)	Reference
1	**1a**	0.1	(a) 		*o*-Xylene/K_2CO_3	130	16	{82}	[47]
2	**27**	1.0	(d) 	”	Toluene/K_2CO_3	130	18	6	[48]
3	”	”	”	”	DMA/Cs_2CO_3	110	18	6	[49]
4	”	”	(n) 	”	”	”	”	76	[49]
5	”	”	(a) 	”	”	”	”	100	[49]
6	**29** + $[NBu_4]Br$ (200 eq.)	0.1	(n) 	”	DMF:H_2O (19:1)/K_2CO_3	160	2	28	[51]
7	**29** + $[NBu_4]Br$ (40 eq.)	0.5	(d) 	”	”	”	6	40	[51]
8	**29** + $[NBu_4]Br$ (400 eq.)	0.05		”	”	130	1	>99	[51]
9	”	0.05		”	”	”	3	98	[51]

[a] a: activated, n: non-activated, d: deactivated (with respect to oxidative addition).
[b] DMA: *N*,*N*-dimethylacetamide, DMF: *N*,*N*-dimethylformamide, NMP: *N*-methylpyrolidone.



Scheme 8. Putative mechanism for the reductive ring-opening of an imine-based palladacycle with phenylboronic acid.

The sulphur-based palladacyclic complex **31** has also been shown to give some, albeit limited, activity in the coupling of the deactivated aryl chloride 4-chloroanisole [54].



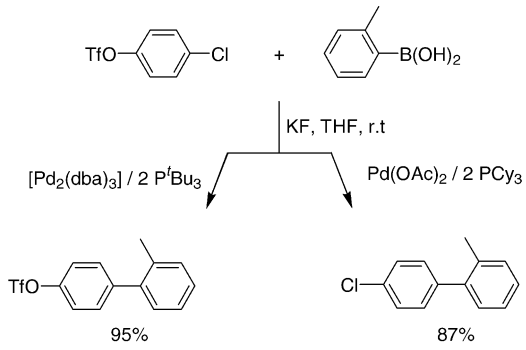
31

3.2. Phosphines

As with the Heck reaction palladium complexes with relatively simple phosphine ligands, either preformed or formed *in situ* have been used with considerable success in the Suzuki coupling of aryl chloride substrates. In general much of the attention has focused on the use of bulky, strongly electron-donating phosphines since these render the palladium centre(s) electron-rich and thus more readily able to activate the strong C–Cl bond.

Shen showed that the simple tricyclohexylphosphine complex $[PdCl_2(PCy_3)_2]$ could be used to couple a range of activated aryl chlorides with aryl boronic acids (e.g. Table 5, entries 1 and 2) [55]. Tricyclohexylphosphine is particularly attractive since it is commercially available, relatively inexpensive and is no where near as air sensitive as tri-*tert*-butylphosphine.

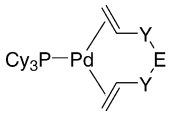
Littke and Fu also found that PCy_3 complexes formed *in situ* with $[Pd_2(dba)_3]$ can be used to couple the non-activated substrate 4-chlorotoluene, but that even better activity is observed when P^tBu_3 is used in place of PCy_3 (entries 3 and 4) [56]. Once again it was found that the handling problems due to the air-sensitivity of P^tBu_3 can be circumvented by its replacement with the stable phosphonium salt $[HP^tBu_3][BF_4]$ [31]. Changing the palladium precursor to palladium acetate and the base to KF leads to considerable improvements in the performance of P^tBu_3-based systems [57]. In addition, Fu and co-workers demonstrated that the ratio of P:Pd is important; whilst a ratio of 1:1 gives optimal activity, increasing the ratio to 2:1 is highly deleterious to the rate of catalysis. With these improvements on board Fu showed that P^tBu_3-based systems can be used to couple activated aryl chlorides at room temperature (e.g. entry 5), while deactivated and non-activated aryl chlorides can be coupled with aryl and alkyl boronic acids at higher temperatures (e.g. entries 6 and 7). This system also allows the formation of biaryls with up to three *ortho*-substituents, although in such cases better results are obtained when the phosphine is replaced with PCy_3 (entry 8). Generally, the order of activity of coupling of aryl halides



Scheme 9.

and triflates is I > Br ≳ OTf ≫ Cl, however when the Pd/P^tBu_3 system is used in the coupling of 4-chlorophenyltriflate, then the chloride is activated with excellent selectivity (Scheme 9). By contrast a PCy_3-containing analogue gives the expected selectivity.

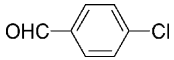
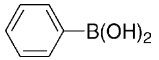
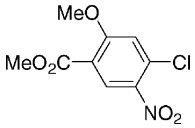
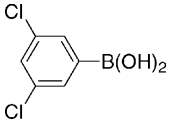
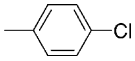
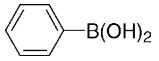
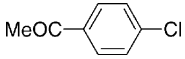
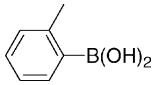
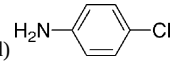
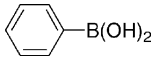
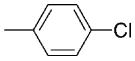
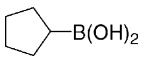
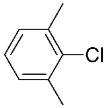
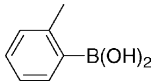
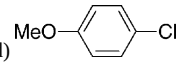
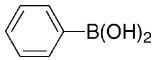
From the data above, it looks as if PCy_3 complexes are not as active as P^tBu_3-based systems in the Suzuki coupling of aryl chlorides, although they are useful for the synthesis of tri-*ortho*-substituted biphenyls. However this may have more to do with the stability of the *in situ*-formed active catalyst species, rather than an inherent lower activity with PCy_3-containing catalysts. Given that it is believed that in many aryl chloride coupling reactions catalysed by palladium complexes with bulky phosphines, the active catalyst is a mono-phosphine species, the larger the phosphine, the higher the stability of the active catalyst with respect to decomposition. Indeed Beller showed that the well defined Pd(0)–mono-tricyclohexylphosphine complexes **32** show considerably enhanced activity in the coupling of deactivated aryl chlorides with phenylboronic acid compared with catalysts formed *in situ* from a palladium acetate or dipalladium tris(benzylideneacetone) and PCy_3 under identical conditions (entries 9–12) [58]. In addition, PCy_3-adducts of palladacycles typically show much higher activity than P^tBu_3-containing analogues (see Section 3.4 below).



32a: Y = $SiMe_2$; E = O
b: Y = CH_2; E = NH
c: Y = CH_2; E = O

One of the most significant advances in the coupling chemistry of aryl chlorides was brought about by Buchwald's development of dialkyl(*o*-biphenyl) ligands. This arose from work on BINAP and the related ligand 2,2′-bis(dicyclohexylphosphino)-1,1′-binapthyl which led to the

Table 5
Selected Suzuki coupling reactions with aryl chloride substrates catalysed by simple phosphine-containing systems

Entry	Catalyst	Catalyst loading (mol% Pd)	Chloride substrate (a, n, d)[a]	Boronic acid	Solvent[b]/base	Temperature (°C)	Time (h)	Conversion {isolated yield} (%)	Reference
1	$[PdCl_2(PCy_3)_2]$	5.0	(a) 		NMP/CsF	100	10	{91}	[55]
2	”	”	(a) 		”	”	”	{77}	[55]
3	$[Pd_2(dba)_3]$ + 2.4PCy_3	3.0	(n) 		Dioxane/Cs_2CO_3	80	5	75	[56]
4	$[Pd_2(dba)_3]$ + 2.4P^tBu_3	”	”	”	”	”	”	86	[56]
5	$[Pd_2(dba)_3]$ + 2P^tBu_3	1.0	(a) 		THF/KF	r.t.	6	{99}	[57]
6	$[Pd_2(dba)_3]$ + 3P^tBu_3	3.0	(d) 		”	90	29	{82}	[57]
7	”	”	(n) 		”	100	37	{75}	[57]
8	$[Pd_2(dba)_3]$ + 2.8PCy_3	3.0			THF/KF	60	48	{89}	[57]
9	**32c**	0.05	(d) 		THF/ K_3PO_4:KF (1:1)	100	22	56	[58]
10	$[Pd_2(dba)_3]$ + 2PCy_3	”	”	”	”	”	”	5	[58]
11	$Pd(OAc)_2$ + PCy_3	”	”	”	”	”	”	8	[58]
12	$Pd(OAc)_2$ + 2PCy_3	”	”	”	”	”	”	28	[58]

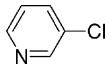
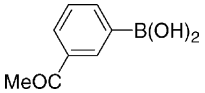
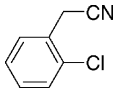
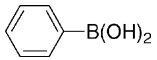
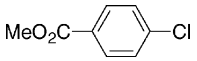
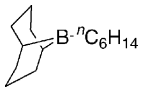
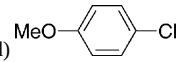
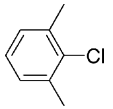
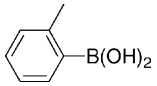
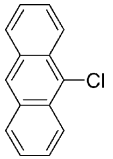
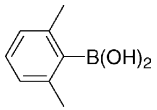
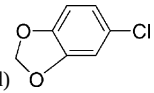
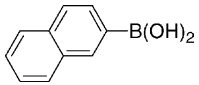
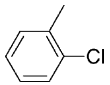
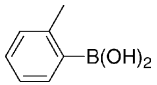
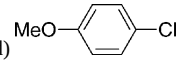
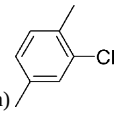
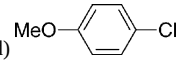
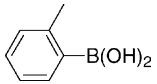
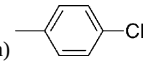
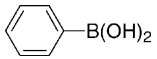
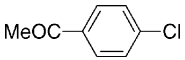
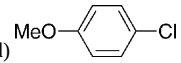
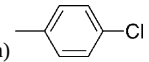
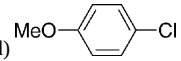
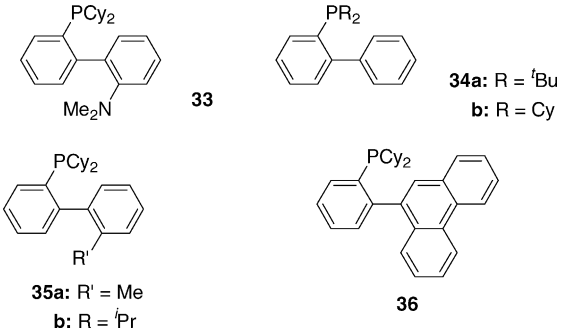
13	$Pd(OAc)_2$ + 1.5 **33**	2.0	”	”	Dioxane/CsF	r.t.	19–30 (not specified)	{92}	[59]
14	$Pd(OAc)_2$ + 2 **34a**	1.5	”	”	THF/KF	r.t.	21	{92}	[60]
15	”	1.0	(a) 		”	”	9	{94}	[60]
16	”	”	(n) 		”	”	20	{91}	[60]
17	”	0.5	(a) 		”	65	20	{83}	[60]
18	$Pd(OAc)_2$ + 1.5 **33**	2.0	(d) 	”	Dioxane/CsF	50	22	{88}	[59]
19	$Pd(OAc)_2$ + 4 **35a**	1.0			Toluene/K_3PO_4	100	3	{92}	[60]
20	$[Pd_2(dba)_3]$ 1.2 **36**	1.0			Xylene/K_3PO_4	110	18–48 (not specified)	{82}	[61]
21	$[Pd(dba)_2]$ + 3 **39a**	1.0	(d) 		Dioxane/CsF	100	7	{96}	[64]
22	”	2.0	(n) 		Toluene/CsF	105	13	{91}	[64]

Table 5 (*Continued*)

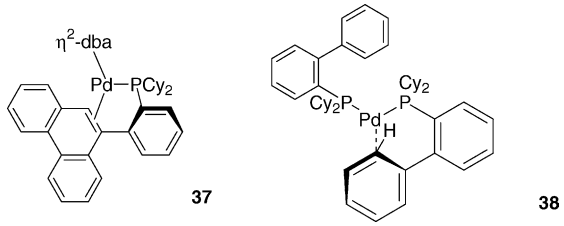
Entry	Catalyst	Catalyst loading (mol% Pd)	Chloride substrate (a, n, d)[a]	Boronic acid	Solvent[b]/base	Temperature (°C)	Time (h)	Conversion {isolated yield} (%)	Reference
23	$[Pd(dba)_2]$ + 2 **43**	1.0	(d) 	”	Toluene/KF	80	72	{99}	[66]
24	”	2.5	(n) 	”	Dioxane/Cs_2CO_3	100	72	{80}	[66]
25	$[Pd_2(dba)_3]$ + 2 **44**	3.0	(d) 		Toluene/K_3PO_4	70	24	{88}	[67]
26	$[Pd_2(dba)_3]$ + 2 **45a**	3.0	(n) 		Dioxane/Cs_2CO_3	60	5	89	[69]
27	$[\{PdCl(C_3H_5)\}_2]$ + **47**	0.1	(a) 	”	Xylene/K_2CO_3	130	20	95	[70]
28	$Pd(OAc)_2$ + **50**	5.0	”	”	THF/KF	r.t.	48–60 (not specified)	{50}	[71]
29	”	”	(d) 	”	”	”	”	{42}	[71]
30	$Pd(OAc)_2$ + 10 **51**	1.0	(n) 	”	Toluene/NaOH	120	18	45	[72]
31	$[Pd_2(dba)_3]$ + **52**	Not specified	(d) 	”	Dioxane/CsF	100	12	{97}	[74]
32	$Pd(OAc)_2$ + **53**	8.0	”	”	Toluene/Cs_2CO_3	80	18	{90}	[75]

[a] a: activated, n: non-activated, d: deactivated (with respect to oxidative addition).
[b] NMP: *N*-methylpyrolidone.

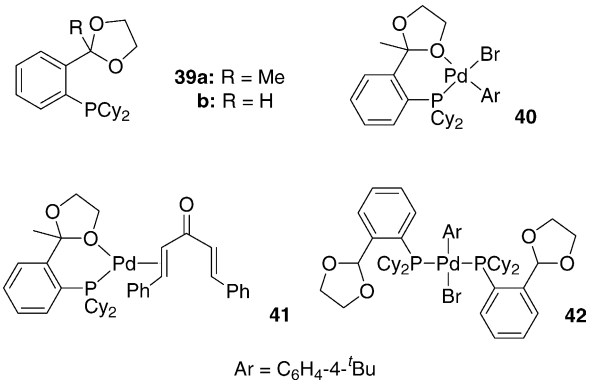
synthesis of the new ligand **33** [59]. A palladium complex of this ligand showed, for the first time, good activity in the Suzuki coupling of deactivated aryl chloride substrates at room temperature (e.g. entry 13). Further modification led to the synthesis of the desamino ligands **34** [60]. The bulkier *tert*-butyl containing analogue **34a** is even more active than ligand **33** in the Suzuki coupling of a wide range of aryl and heteroaryl chlorides at room temperature (e.g. entries 14–16). In addition, these catalyst systems can be used to couple alkyl boronic acids with aryl chlorides (e.g. entries 17 and 18) [59,60].The dicyclohexylphosphino ligands **34b**, **35a** and **35b** give catalysts that are more active in the coupling of sterically hindered substrates and can be used to produce biaryls with up to three *ortho*-substituents (e.g. entry 19) [60]. Subsequently, the synthesis of the highly bulky ligand **36** allowed the formation of biaryl containing four *ortho*-substituents (e.g. entry 20).



The efficiency of these dialkyl(*o*-biphenyl)phosphine ligands was attributed to their relatively high basicity, which would facilitate oxidative addition; their size and the fact that the secondary ring of the biphenyl function may coordinate to the palladium centre(s). Such an interaction may help stabilise low-coordinate complexes with respect to decomposition. In addition it would increase crowding around the palladium centre(s), thus facilitating reductive elimination. Further, such an interaction may aid reductive elimination as it would effectively force the two σ-aryl ligands perpendicular to the coordination plane, an arrangement that has been suggested to favour reductive elimination in platinum complexes [62]. Evidence for such interactions was provided by the crystal structure of the complex **37**, formed from ligand **36** and $[Pd_2(dba)_3]$, which shows an η^2-arene interaction with the palladium centre(s). An alternative coordination mode was recently reported by Fink and co-workers who showed that reaction of $[Pd_2(dba)_3]$ with the ligand **34b** gives the zerovalent bisphosphine complex **38** which contains an unusual η^1-arene interaction [63].

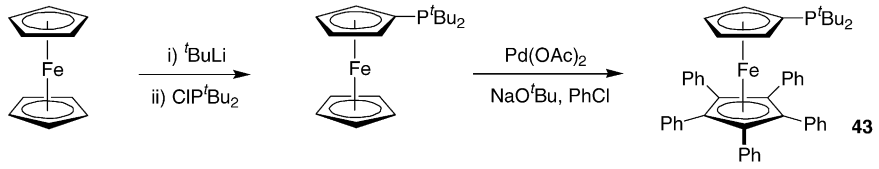


Bei et al. developed a novel class of phosphine ligand typified by **39**, which are notionally related to the ligand developed by Buchwald in that they have a 2-functionalised aryl substituent on a dialkylphosphine residue. Palladium complexes of the ligand **39a** prove to be active catalysts for the Suzuki coupling of a range of aryl chloride and aryl boronic acid substrates (e.g. entries 21 and 22) [64]. By contrast, the less bulky phosphine ligand **39b** shows somewhat lower activity. The authors attributed this difference in activity with minor ligand variation, to the formation of structurally distinct catalytically active species. The reaction of $[Pd(dba)_2]$ with 4-*tert*-butylbromobenzene and ligand **39a** gives the complex **40** in which there is a discreet O–Pd bond which is maintained in solution [65]. Further, reaction of **39a** with $[Pd(dba)_2]$ in the absence of an aryl halide generates the palladium(0) complex **41** which also contains a Pd–O bond. By contrast, the ligand **39b** reacts with $[Pd(dba)_2]$ and 4-*tert*-butylbromobenzene to generate the complex **42** which contains no Pd–O interaction. Thus, it appears as if a seemingly minor structural modification can lead to major differences in the types of complexes that the ligands **39a** and **39b** can form, consequently it is likely that the active catalysts formed from these ligands are significantly different.



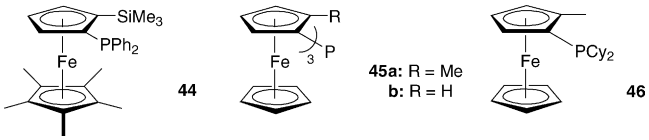
Another class of ligand that has proved effective in aryl chloride coupling reactions are those with ferrocenyl substituents. While the bulky ligand **43** appears to be structurally rather elaborate, it is in fact produced in three steps from ferrocene (Scheme 10) [66]. A catalyst formed from **43** and $[Pd(dba)_2]$ is active in the Suzuki coupling of electronically deactivated and sterically hindered aryl chlorides (e.g. entries 23 and 24).

Interestingly, the structurally related, but far less electron-donating tri*aryl*phosphine ligand **44**, was reported by Fu and co-workers to be an active catalyst for a range of aryl chloride Suzuki couplings (e.g. entry 25), despite the fact that the ligand is far less electron-donating than di- or trialkylphosphines [67]. Richards and co-workers investigated the use of the triferrocenyl phosphine ligand **45a** in the coupling of non-activated and activated substrates (e.g. entry 26) and found the activity to be comparable to the use of tri-*tert*-butylphosphine under identical conditions. This is despite the fact that, as a triarylphosphine, **45a** is far less basic [68,69]. Indeed, a catalyst formed from the more electron-donating

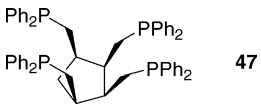


Scheme 10.

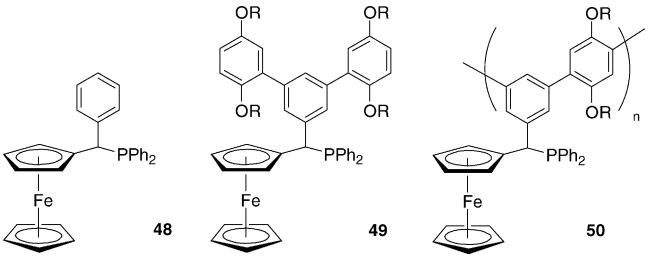
dialkylferrocenyl phosphine **46** shows lower activity. The size of the ligand is important; a catalyst containing the unmodified triferrocenylphosphine **45b** shows very poor activity.



Further evidence that high σ-basicity is not necessarily a prerequisite is provided by the observation that the tetra(diaryl)phosphine **47** can be used to couple activated aryl chloride substrates (e.g. entry 27) [70].

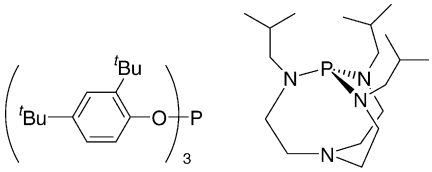


The water has been muddied even further in the arguments on what electronic properties a ligand should have in order to facilitate coupling of aryl chlorides by an elegant piece of research by Hu et al., which shows that a 'macro-molecular' effect can come into play [71]. Thus, whilst complexes formed *in situ* from the mononuclear model diarylphosphines **48** and **49** show no activity, the analogous polymeric phosphine **50** can be used to reasonable effect to couple activated and deactivated aryl chlorides at room temperature (e.g. entries 28 and 29)!



So, it seems as if simple arguments based on how electron-donating a ligand is do not satisfactorily explain why some catalysts are active with aryl chloride substrates while others are not. Part of the problem may be one of perception — many more catalysts than were previously supposed are able to activate aryl chlorides, indicating that the process is perhaps not as difficult as it is often assumed to be. This is particularly true for activated and even non-activated aryl chlorides, which can even be activated by catalysts containing ligands as poorly electron donation as the bulky phosphite **51** (entry 30) [72]. It is possible in this case that the activity may be due to hydrolysis of the ligand in the presence of the strong base. Indeed, it has been shown that such hydrolytic processes can have a bearing on the Suzuki coupling of aryl bromide substrates, giving complexes with $R_2P(OH)$ ligands (R = OAr) [73]. Complexes formed *in situ* from the secondary phosphine oxide systems such as $P(=O)H^tBu_2$, **52**, by virtue of their equilibrium with hydroxyphosphines (Eq. (3)) have been shown by Li to couple aryl boronic acids with deactivated aryl chloride substrates (e.g. entry 31) [74].

Verkade and co-workers have recently shown that although it has to be used in somewhat higher loadings than comparable trialkylphosphines, the bicyclic aminophosphine **53** can be used to couple both electron poor and rich aryl chlorides with phenylboronic acid (e.g. entry 32) [75].

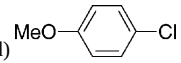
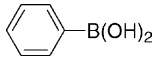
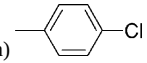
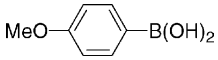
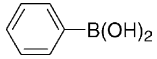
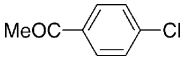
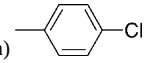
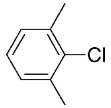
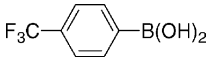
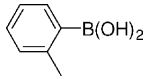


It is probable that the future development of phosphines that show good activity in the Suzuki coupling of aryl chloride substrates will highlight the importance of secondary interactions, such as those shown by the ligands **33**–**36**, **39a** and, almost certainly, **50**, in catalyst performance, particularly with regard to catalyst longevity. This is an issue which we will address further in Section 3.4.

3.3. Carbenes

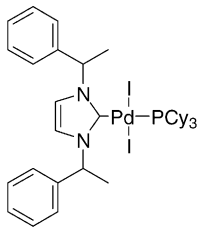
As with the Heck reaction, the notional relationship between heterocyclic carbenes and trialkylphosphines due to their high σ-basicity and low π-acidity has encouraged the study of these ligands in the Suzuki coupling of aryl chlorides. Again it was Herrmann et al. who first reported the potential utility of carbene complexes in these reactions, for example they found that the complex **18a** could be used to reasonable effect with activated substrates such as 4-chloroacetophenone [38]. Subsequently, they demonstrated that the mixed phosphine-carbene complexes of the type **54** are much more active and can be used for the coupling of activated, non-activated and even deactivated aryl chlorides (e.g. Table 6, entry 1) [76]. Replacement of the PCy_3 with PPh_3 is deleterious to activity, presumably due to the lowering of electron density on the palladium centre(s). Likewise, the bis-carbene complex **55** shows no activity in the coupling of 4-chloroanisole with phenylboronic acid, demonstrating the importance of the PCy_3 co-ligand. Indeed, when the result

Table 6
Selected Suzuki coupling reactions with aryl chloride substrates catalysed by simple carbene-containing systems

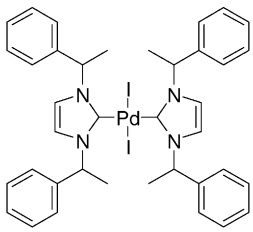
Entry	Catalyst	Catalyst loading (mol% Pd)	Chloride substrate (a, n, d)[a]	Aryl boronic acid	Solvent/base	Temperature (°C)	Time (h)	Conversion {isolated yield} (%)	Reference
1	**53**	1.0	(d) 		Xylene/Cs_2CO_3	130	32	69	[76]
2	$[Pd_2(dba)_3]$ + **56**	3.0	(n) 	”	Dioxane/Cs_2CO_3	80	1.5	{96}	[77]
3	$[Pd_2(dba)_3]$ + **57**	3.0	”		”	”	1.5	{99}	[77]
4	$Pd(OAc)_2$ + **59**	2.5	”		”	”	1.5	99	[80]
5	**19**	3.0	(a) 	”	”	”	1.5	{74}	[40]
6	**61b**	”	(n) 	”	”	”	1	68	[80]
7	$Pd(OAc)_2$ + carbene formed from **62**[b]	3.0			THF/CsF	r.t.	24	{85}	[82]
8	”	”	”		THF:H_2O (10:1)/KO^{t}Bu	60	”	{66}	[82]

[a] a: activated, n: non-activated, d: deactivated (with respect to oxidative addition).
[b] Formed *in situ* by reaction of **62** with KH/KO^{t}Bu.

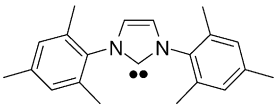
obtained with complex **53** is compared with that with the mono-PCy_3 complex **32c** (Table 5, entry 9) it is tempting to conclude that the function of the carbene complex is to act simply as a source of a mono-PCy_3-containing active catalyst. This would require that the carbene is lost during catalyst activation — carbene lability will discussed later (Section 5.2).



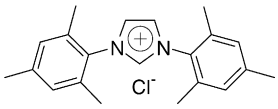
54



55



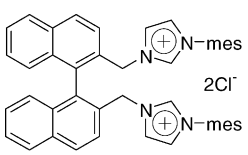
56



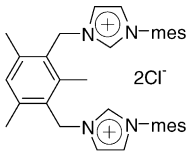
57

Increasing the size of the substituents on the carbene ligand has been found to be beneficial to the activity in the Suzuki coupling of aryl chlorides. Nolan and co-workers showed that the carbene ligand **56**, which is both more sterically demanding and electron-donating than PCy_3 can be used to good effect in the coupling of the non-activated substrate 4-chlorotoluene with phenylboronic acid (entry 2) [77]. Judicious choice of base not only facilitates the reaction but allows *in situ* deprotonation of the air-stable parent imidazolium salt **57**, obviating the need to pre-synthesise and handle the sensitive carbene ligand. The resultant catalyst system can be used to couple a range of aryl chloride and aryl boronic acid substrates (e.g. entry 3).

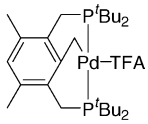
Zhang and Trudell investigated the use of a range of potentially chelating bis-carbene complexes formed *in situ* from bis-imidazolium salts [78]. Two such species in particular showed good activity, **58** and **59**, with the latter being used to couple a range of substrates (e.g. entry 4). In this latter case, it is not currently possible to exclude the involvement of a bis-carbene 'pincer' complex *via* C–H activation of the 2-methyl group on the mesityl linker. Indeed, the related bis-phosphine complex **60** is catalytically active in the Heck coupling of aryl bromides and iodides [79].



58



59

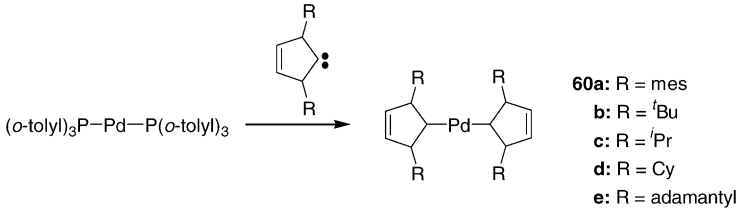


60

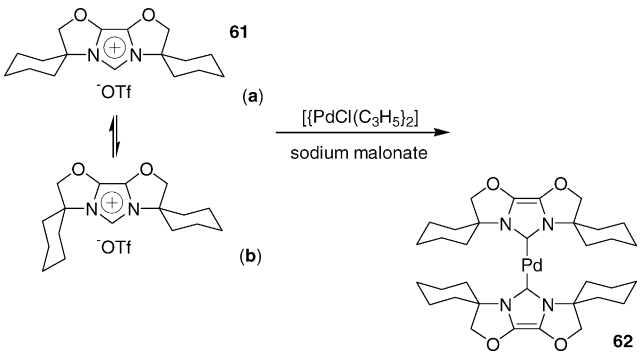
The bidentate *C,N*-carbene ligand-containing complex **19** has been tested in the Suzuki coupling of activated aryl chlorides (e.g. entry 5) [40]. Unlike with its application in the Heck coupling of aryl chlorides, it is not necessary to add TBAB in order to maximise activity.

A reasonably general method for the synthesis of palladium(0) bis-carbene complexes **61** was developed by Herrmann and co-workers, by the displacement of the phosphine ligands of $[Pd\{P(o\text{-tolyl})_3\}_2]$ (Scheme 11) [80]. The resultant complexes were found to show somewhat different behaviour to complexes formed *in situ* from $[Pd_2(dba)_3]$ and the corresponding imadazolium salts. Thus, the complex **61a** shows no activity in the coupling of 4-chlorotoluene with phenyl boronic acid, in contrast with a catalyst formed *in situ* from the imidazolium salt **57**. Conversely, while complex **61b** is active in this reaction (entry 6), the system formed *in situ* from $[Pd_2(dba)_3]$ and *N,N′*-di-*tert*-butyl-imidazolium chloride is inactive.

The synthesis of the highly sterically encumbered complex **61e** allowed for the Suzuki coupling of aryl chloride substrates at room temperature [81]. While this works well for sterically unencumbered substrates, the use of *ortho*-substituted aryl chlorides leads to a substantial drop in performance. Glorius and co-workers reasoned that in order for a carbene ligand to be large enough to facilitate reductive elimination yet small enough to allow oxidative addition of an encumbered aryl chloride, bulky, yet flexible *N*-substituents are necessary [82]. They synthesised the new imadazolium salt **62**, which they showed to be in equilibrium between the two forms (**a**) and (**b**) in solution, and the bis-carbene complex **63**. While the preformed complex **63** proved to be catalytically inactive at room temperature, a catalyst formed *in situ* from **62** and palladium acetate was able to couple sterically hindered aryl chlorides with ease under these conditions (e.g. entry 7). Increasing the temperature allows the formation of tri-*ortho*-substituted biaryls (entry 8).

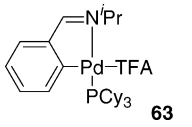


Scheme 11.

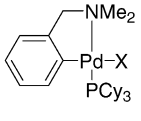


3.4. Phosphine adducts of palladacycles

The mechanism shown in Scheme 8 shows how palladacycles can undergo a reductive ring opening process. We have shown this process also occurs with a triphenylphosphine adduct of the palladacycle [53]. We reasoned that palladacycles can act as an air-stable, robust, clean sources for the highly efficient delivery of low coordinate palladium(0) phosphine species. Given that PCy_3-containing complexes can act as catalysts for the Suzuki coupling of aryl chlorides, depending on the precise nature of the precatalyst, and given the comparatively low cost and air-sensitivity of this ligand we decided to explore the use of tricyclohexylphosphine adducts of *N*-based palladacycles as precatalysts. The complexes **64** and **65** both show very good activity in the Suzuki coupling of a range of activated, non-activated and deactivated aryl chlorides at low catalyst loadings (e.g. Table 7, entries 1–3) [83,84]. Typically, there is not a great deal of difference in activity between the imine and amine palladacycles, however since *N*,*N*-dimethylbenzylamine is commercially available and cheap, it represents the better choice. Variation of the anionic ligand 'X' is found to have some effect with the approximate order Cl ∼ Br > TFA ∼ OTf > I.

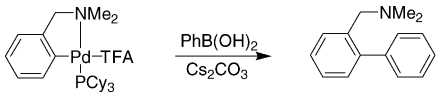


63



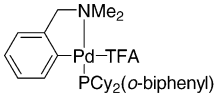
64a: X = TFA
b: X = Cl
c: X = Br
d: X = I
e: X = OTf

Evidence that an activation mechanism related to that outlined in Scheme 8 is likely to be operative under catalytic conditions was obtained from the reaction performed at 60 °C, which showed the formation of substantial amounts of the 2-phenylated amine *N*,*N*-dimethyl(2-phenyl)benzylamine (Eq. (5)), presumably by a reductive ring-opening of the orthometallated dimethylbenzylamine complex. The active catalysts generated in this process would, in the first instance be "Pd-PCy_3", obviously the solvent would play a stabilising role for this complex but decomposition may be fairly rapid. Indeed a study of conversion against time using **65a** as a catalyst in the coupling of 4-chloroanisole with phenylboronic acid shows an induction time of about 1 h followed a period of 30 min rapid activity, followed quickly by catalyst deactivation [85].

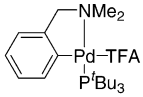


(5)

If the function of the palladacycle is essentially efficient, sacrificial generation of low-coordination palladium phosphine complexes, then such catalyst precursors might prove useful as 'standard' indicators of a phosphine performance. Such a study was performed using the phosphine complexes **66** and **67** — the latter of which was prepared *in situ* from the parent palladacycle and P^tBu_3 due to the high lability of the complex [84].



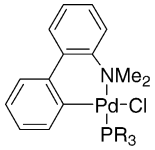
65



66

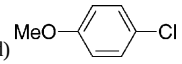
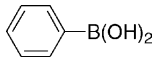
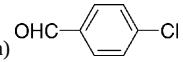
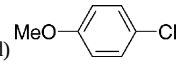
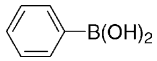
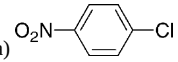
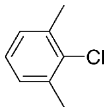
Interestingly, activity in the coupling of 4-chloroanisole falls in the order **65a** > **66** > **67**, supporting the argument that PCy_3 can be an excellent ligand for the Suzuki reaction, provided the correct palladium source is used. Comparative studies with $[Pd_2(dba)_3]$ and palladium acetate as the palladium sources showed that palladium acetate is the better of these precursors [86]. Further, the order of activity with respect to the ligand changes when palladium acetate is used as the palladium source with PCy_2(*o*-biphenyl) (**34b**) showing the best activity and PCy_3 the worst. Systems with the ligand **34b** give similar results regardless of whether palladium acetate or a palladacyclic precursor is used as the palladium source. An unusual difference in the effect of ligand:metal ratio is seen with the three phosphine ligands tested. With the PCy_3 and P^tBu_3 containing systems **65a** and **67** optimum performance is seen with a P:Pd ratio of 2:1 — addition of further equivalents of the phosphine to either catalyst system is highly deleterious with nearly all activity lost when the ratio reaches 3:1. By contrast, increasing the amount of added ligand **34b** to the precatalyst system is not deleterious, with optimal activity seen at between three and four phosphines per palladium. This data fits with the formation of low-coordinate active catalysts. In the case of PCy_3 and P^tBu_3, addition of too much phosphine leads to over-coordination which 'switches off' activity. It is possible that with ligand **34b**, interaction of the secondary aryl ring with the palladium centre(s) (see above, Section 3.2) prevents catalyst deactivation by 'over-coordination'. Therefore, the addition of excess ligand would merely serve to reverse any dissociation equilibria, increasing the lifetime of the low-coordinate active species.

Subsequently Indolese and Studer showed that the related palladacyclic complexes **68**, containing either tertiary or secondary alkylphosphine ligands can be used to good effect in the Suzuki coupling of aryl chlorides [87].



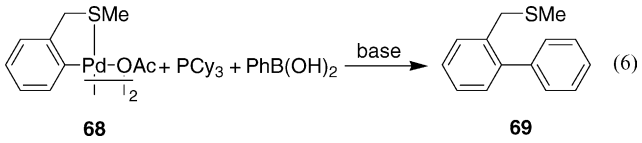
67a: $PR_3 = PCy_3$
b: $PR_3 = PHCy_2$
c: $PR_3 = PH^tBu_2$
d: $PR_3 = PH(nor)_2$

Table 7
Selected Suzuki coupling reactions with aryl chloride substrates catalysed by phosphine and carbene adducts of palladacycles

Entry	Catalyst	Catalyst loading (mol% Pd)	Chloride substrate (a, n, d)[a]	Aryl boronic acid	Solvent /base	Temperature (°C)	Time (h)	Conversion {isolated yield} (%)	Reference
1	**65a**	0.01	(d) 		Dioxane/Cs_2CO_3	100	17	80	[83]
2	”	1.0	”	”	”	60	”	97	[83]
3	”	0.001	(a) 	”	”	100	”	99	[83]
4	**69** + 2 **34b**	0.1	(d) 		”	”	18	62	[88]
5	**72** + 2 PCy_3	0.001	”	”	”	”	48	90	[89]
6	”	0.00005	(a) 	”	”	”	”	100	[89]
7	”	0.0005		”	”	”	”	58	[89]

[a] a: activated, n: non-activated, d: deactivated (with respect to oxidative addition).

It is not necessary to use a nitrogen-based palladacycle, catalysts formed *in situ* from the sulphur-based palladacycle **69** and either PCy_3, P^tBu_3 or ligand **34b** can be used to good effect (e.g. entry 4) [88]. Again, the same general trends are observed on increasing the P:Pd ratio as described above. A similar activation process is probably operative as demonstrated by the reaction of complex **69**, in the presence of PCy_3, with phenylboronic acid and base which yields the thioether **70** (Eq. (6)).



(6)

From the discussion of catalyst activation presented above, it may be concluded that there would be no benefit in producing a trialkylphosphine adduct of an orthopalladated triarylphosphite complex, since the eliminated ligand would be a triarylphosphite — a good ligand for Pd(0). This would mean that the palladium centre(s) in the resultant mixed trialkylphosphine–triarylphosphite complex would not be as electron rich as a simple trialkylphosphine-containing species, therefore oxidative addition (the rate-determining step) would be slower. However when an *in situ* formed PCy_3 adduct of complex **10** is used then it proves to be extremely active compared with the amine-based palladacycle **65a** [85]. The increase in overall performance is explained, not in terms of higher rates of catalysis, but rather by substantially increased catalytic activity — while **65a** is only active for about 30 min, 10/PCy_3 is active for over 24 h. Therefore, it seems likely that the function of the π-acidic phosphite ligand is to stabilise the Pd(0) catalyst resting state. If this is true, then longevity should vary with the π-acidity of the co-ligand. This indeed proves to be the case, as can be seen in Fig. 1, where the highest TON results from the precatalyst with the most π-acidic co-ligand, complex **72**, despite the fact that this system shows the lowest maximum rate [89,90]. This catalyst system shows excellent activity in the coupling of a range of deactivated to activated and sterically hindered aryl chlorides at extremely low palladium loadings (e.g. entries 5–7).

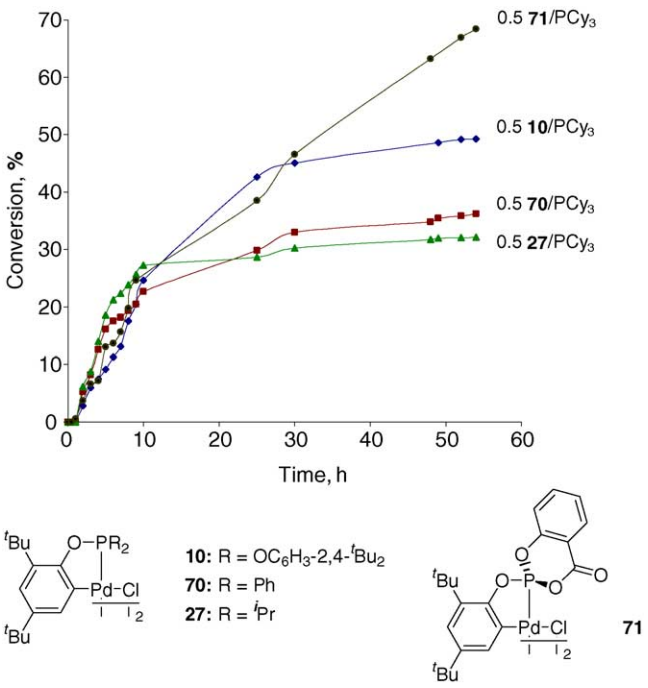


Fig. 1. Plot of conversion against time in the Suzuki coupling of 4-chloroanisole with phenylboronic acid at 0.001 mol% Pd loading. Conditions: Cs_2CO_3, 1,4-dioxane, 100 °C.

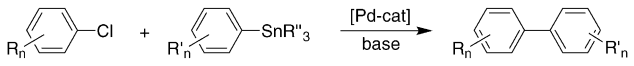
4. Catalysts for other C–C bond forming reactions

4.1. The Stille reaction

The Stille coupling of aryl chlorides (Scheme 12) has not been developed to the same extent as the Suzuki reaction. This may partly be due to the fact that the Stille reaction is perceived to be a less useful process due to the toxicity of the tin reagents. However, the design of catalysts that can facilitate this reaction is still desirable as it remains widely used.

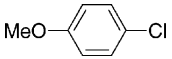
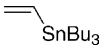
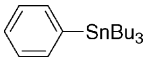
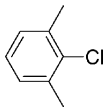
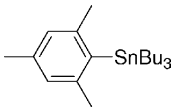
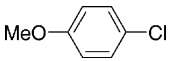
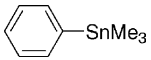
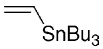
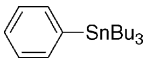
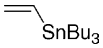
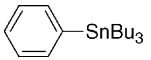
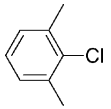
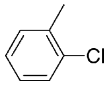
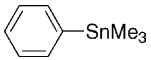
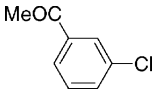
Fu demonstrated that Pd/P^tBu_3 complexes can be used in a range of couplings of aryl chlorides with both vinyl and aryl tin reagents (e.g. Table 8, entries 1 and 2), the best activity results when cesium fluoride is used as the base [91,92]. In order to avoid the issue of the air-sensitivity of the phosphine, the authors investigated the use of the air-stable bis-phosphine complex [Pd(P^tBu_3)$_2$], **11**, and found that it could be used to excellent effect, even in the synthesis of sterically challenging tetra-*ortho*-substituted biphenyls (e.g. entry 3). Alternatively, the air-stable phosphonium salt [HP^tBu_3][BF_4] can be used as a replacement for the P^tBu_3 [31]. As seen with the Suzuki reaction (see Section 3.2 above), the use of Pd-P^tBu_3 in the coupling of 4-chlorophenyl triflate leads exclusively to the activation of the C–Cl bond [92].

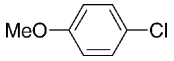
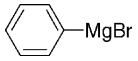
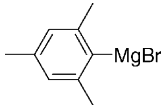
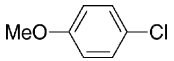
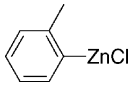
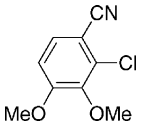
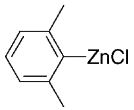
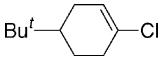
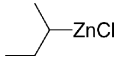
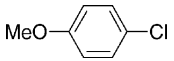
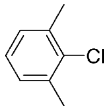
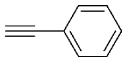
Grasa and Nolan have tested a carbene complex formed *in situ* from palladium acetate and the imidazolium salt **24** and found that reasonable activity results when tetrabutylammonium fluoride (TBAF) is used as the base. Thus, a range of activated to deactivated aryl chlorides can be coupled with



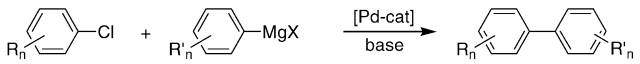
Scheme 12. The Stille coupling of aryl chlorides.

Table 8
Selected Stille, Negishi, Kumada and Sonogashira coupling reactions with aryl chloride substrates

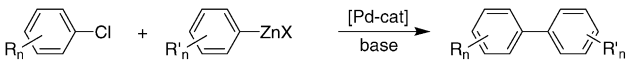
Entry	Catalyst	Catalyst loading (mol% Pd)	Chloride substrate (a, n, d)[a]	Coupling partner	Solvent[b]/base	Temperature (°C)	Time (h)	Conversion {isolated yield} (%)	Reference
1	$[Pd_2(dba)_3]$ + 2 P^tBu_3	3.0	(d) 		Dioxane/CsF	100	48	90	[92]
2	”	”	”		”	”	”	{94}	[92]
3	**11**	3.0			”	”	15	{89}	[92]
4	$Pd(OAc)_2$ + 24	3.0	(d) 		Dioxane/TBAF	”	48	{35}	[93]
5	”	”	”		”	”	24	15	[93]
6	**10** + 4 PCy_3	1.0	”		Dioxane/K_3PO_4	”	18	100	[94]
7	**10** + 4 PCy_3	1.0	”		”	100	18	70	[94]
8	$Pd(OAc)_2$ + 2PCy_3	1.0	”		”	”	”	100	[94]
9	”	”		”	”	”	”	92	[94]
10	**15**	6.0	(n) 		H_2O/Cy_2NMe	140	24	{60}	[96]
11	”	”	(a) 	”	”	”	”	{88}	[96]

12	$[Pd_2(dba)_3]$ + 2 **24**	2.0	(d) 		Dioxane:THF	80	3	{97}	[97]
13			”		”	”	3	{95}	[97]
14	**11**	2.0	(d) 		THF·NMP	100	2	{94}	[99]
15	”	”			”	”	18	{76}	[99]
16	”	”			”	”	5	{86}	[99]
17	$Na_2[PdCl_4]$ + 2P^{t}Bu$_3$ + 0.75CuI	”	(d) 		Xylene	120	14	{84}	[100]
18	”	”			”	”	”	{62}	[100]

[a] a: activated, n: non-activated, d: deactivated (with respect to oxidative addition).
[b] NMP: *N*-methylpyrolidone.



Scheme 13. The Kumada coupling of aryl chlorides.



Scheme 14. The Negishi coupling of aryl chlorides.

both aryl and vinyl tin reagents (e.g. entries 4 and 5) [93]. In general, the results obtained with the carbene complex are not as good as those with P^tBu_3-containing systems.

In view of the extremely high activity and longevity displayed by catalysts formed *in situ* from PCy_3 and the orthopalladated triarylphosphite complex **10** in the Suzuki coupling of aryl chlorides we decided to test this catalyst system in related Stille reactions. While this catalyst does indeed show good activity (e.g. entries 6 and 7) — better than with catalysts containing either P^tBu_3 or the carbene ligand formed from **24**, we were surprised to find that just as good activity results when palladium acetate is used as the palladium source [94]. This simple Pd/PCy_3 system shows the best activity to date with a range of aryl chloride substrates (e.g. entries 8 and 9). Very little change in catalyst performance is observed on changing from activated to non-activated or from small to sterically hindered aryl chloride substrates. This strongly suggests that, unlike in the Suzuki reaction, the rate-determining step is not oxidative addition of the aryl chloride substrate, but rather either transmetallation or reductive elimination. It is unlikely that the latter process is rate-limiting as essentially identical intermediates should be involved in this process as in the Suzuki reaction. This would suggest that the rate-determining step is transmetallation. Indeed it has been shown that the rate of transmetallation of complexes of the type [PdCl(Ar)(P_2)] with organostannanes is very slow [95]. The similar activity of the PCy_3-containing catalysts derived from either complex **10** or palladium acetate suggests that, unlike in the Suzuki reaction catalysed by **10**/PCy_3 mixtures, catalyst longevity and therefore performance is not enhanced by the presence of a π-acidic ligand. This is not surprising if the role of the π-acidic phosphite ligand in the Suzuki reaction is to reversibly coordinate to and stabilise a Pd(0) species. Since the rate-determining step appears to be transmetallation, the resting state species here would be Pd(II). π-Acidic phosphite ligands would not be expected to show any particular propensity to stabilise such Pd(II) resting states, compared with trialkylphosphines.

Recently, Wolf and Lerebours demonstrated that the hydroxyphosphine-containing complex [$PdCl_2${$P(OH)^tBu_2$}$_2$], **15**, can be used in the Stille couple of activated and non-activated aryl chlorides in water (e.g. entries 10 and 11) [96].

4.2. The Kumada reaction

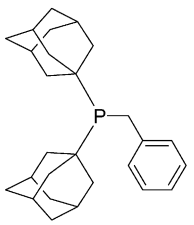
The palladacyclic complex **1a** has been used in the Kumada coupling (Scheme 13) of aryl and alkyl Grignard reagents with chlorobenzene [6d]. Huang and Nolan later demonstrated that a carbene complex formed *in situ* from the imidazolium salt **24** is an effective catalyst for the coupling of aryl Grignard reagents with a range of non-activated, deactivated and sterically hindered aryl chlorides (e.g. entries 12 and 13) [97]. Li has shown that the palladium complexes **15** and **16**, containing hydroxyphosphine ligands, can be used to good effect in the coupling of non activated and deactivated aryl chlorides with aryl Grignards [98].

4.3. The Negishi reaction

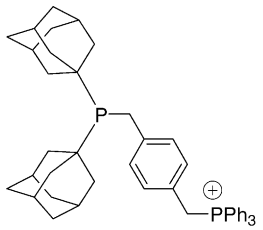
While the palladacyclic complex **1a** can be used in the Negishi coupling (Scheme 14) of organozinc reagents with activated and non-activated aryl chlorides such as 4-chloronitrobenzene [6d], to date only one general catalyst system has been uncovered for the coupling of a wide range of substrates. This is the bisphosphine complex [Pd(P^tBu_3)$_2$], **11**, which Dai and Fu have shown to be active in a wide range of aryl and vinyl chloride couplings with both aryl and alkyl zinc reagents (e.g. Table 8, entries 14–16) [99]. Li has shown that the hydroxyphosphine-containing complex **15** can be used to reasonable effect in the Negishi coupling of aryl chlorides [74b].

4.4. The Sonogashira reaction

Plenio and co-workers recently reported that the bulky trialkylphosphine ligands P^tBu_3 and **73** are both effective for the Sonogashira coupling (Scheme 15) of electron-deficient, electron-rich and sterically hindered aryl chloride substrates (e.g. Table 8, entries 17 and 18) [100]. In an interesting extension of this work, it was shown that the "phase-tagged" phosphine ligand **74** affords some recyclability in the coupling of 4-chloroacetophenone [101].



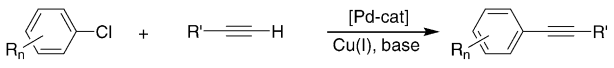
72



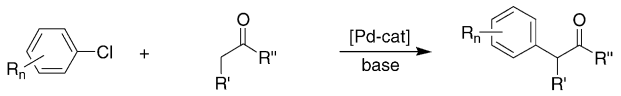
73

4.5. α-Arylation

The enolizable nature of carbonyl compounds containing α-hydrogens allows the anion formed on deprotonation to



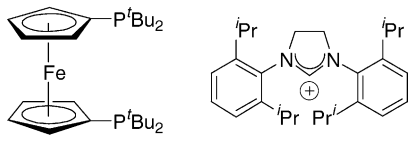
Scheme 15. The Sonogashira coupling of aryl chlorides.



Scheme 16. The α-arylation reaction with aryl chlorides.

undergo coupling reactions — the so called α-arylation reaction (Scheme 16) [102].

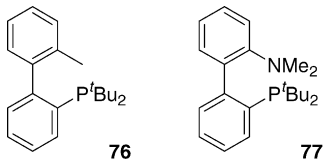
The extension of this reaction to aryl chlorides was originally reported by Kawatsura and Hartwig [103]. While the palladium complex of the ligand **75** could be used to good effect (e.g. Table 9, entry 1) mechanistic studies indicated that mono-de-coordination occurs, implying that the use of bulky monodentate phosphines may be advantageous. This indeed proves to be the case, with both P^tBu_3- and PCy_3-containing complexes showing good activity (e.g. entry 2). The Pd/**75** catalyst system can also be used to couple di-*tert*-butylmalonate with chlorobenzene (entry 3) although no reaction is observed with diethylmalonate. However, changing to either a Pd/**43** or a Pd/P^tBu_2(1-Ad) system with K_3PO_4 acting as base in toluene facilitates such reactions [104]. The Pd/PCy_3 catalyst can be exploited for the synthesis of oxindoles from 2-chloroanilides (e.g. entry 4) [105].



74 **75**

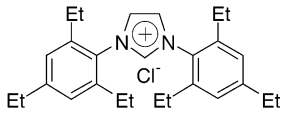
The observation by Hartwig and co-workers that the rate of reductive elimination from arylpalladium enolate complexes is nearly identical for enolates derived from esters and ketones [106] suggested that arylation of esters should be feasible if enolate formation and stability could be optimised. They found that the use of hexamethyldisilazide (HMDS) salts as bases, along with catalysts formed *in situ* from either P^tBu_3 or the carbene ligand obtained *in situ* by deprotonation of the precursor salt **76**, opens up not only the α-arylation of esters by aryl chlorides (e.g. entry 5) but also imine-protected amino acids [107].

Buchwald and co-workers have again demonstrated the utility of phosphines containing the ortho-biphenyl moiety, finding that they give good results in α-arylation reactions with aryl chloride substrates [108–110]. A catalyst system formed *in situ* from palladium acetate and ligand **33** proves to be effective with a range of aryl chlorides (e.g. entry 6), while the use of the bulkier ligand **77** facilitates the α-arylation of nitropropane [108]. Changing the palladium source to dipalladium tris(dibenzylideneacetone) and the base from sodium *tert*-butoxide to cesium carbonate considerably widens the scope of this reaction and allows the use of milder conditions (e.g. entry 7) [110]. A catalyst system based on the ligand **78** can be applied to the α-arylation of esters with aryl chlorides (e.g. entry 8) [109].



76 **77**

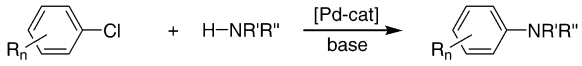
The use of carbene complexes formed *in situ* from imidazolium salts has recently allowed Huang and co-workers to initiate the coupling of aryl chlorides with the malonitrile anion [111]. The imidazolium salts **57** and **79** prove particularly effective amongst those tested (e.g. entry 9).



78

5. Catalysts for the Buchwald–Hartwig amination of aryl chlorides

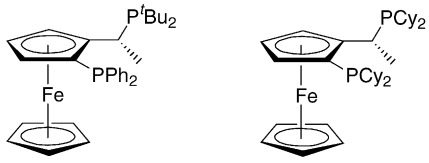
The Buchwald–Hartwig reaction has emerged as a potent method for the catalytic formation of carbon-nitrogen bonds [112]. Understandably, there has been much recent effort expended on the amination of aryl chloride substrates (Scheme 17).



Scheme 17. The Buchwald–Hartwig amination of aryl chlorides.

5.1. Phosphines

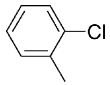
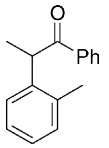
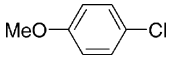
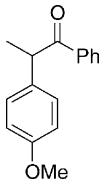
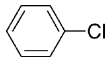
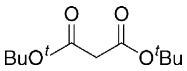
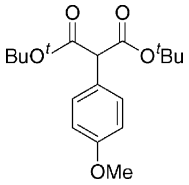
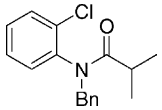
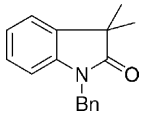
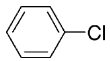
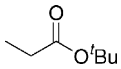
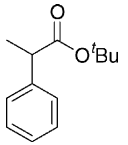
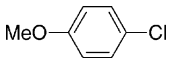
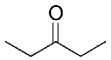
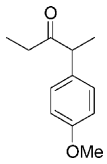
Aryl chloride amination was initiated by Reddy and Tanaka who showed that the simple tricyclohexylphosphine complex $[PdCl_2(PCy_3)_2]$, can be used to couple activated and non-activated aryl chlorides with a range of alkyl, aryl and benzyl amines (e.g. Table 10, entries 1 and 2) [113]. Shortly afterwards Hartwig and co-workers reported the use of chelating ferrocenyl–bisphosphine ligands with bulky substituents — ligands **74**, **80** and **81** [114]. These systems allowed the coupling of a range of amines with non-activated aryl chlorides (e.g. entries 3 and 4). The ligands **80** and **81** both show particularly high selectivity for mono-arylation over di-arylation of primary alkylamines.

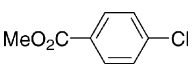
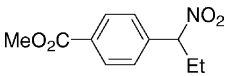
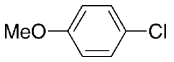
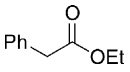
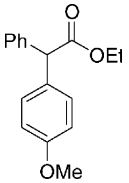
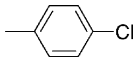
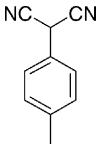


80 **81**

The high activity with these bulky ferrocenyl diphosphines was attributed to their ability to undergo reversible

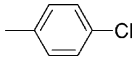
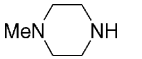
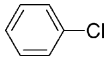
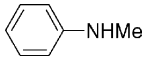
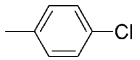
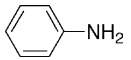
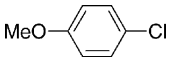
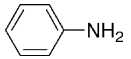
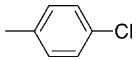
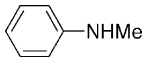
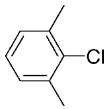
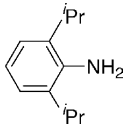
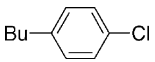
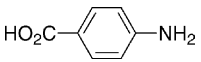
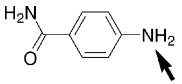
Table 9
Selected α-arylation reactions with aryl chloride substrates

Entry	Catalyst (mol% Pd)	Chloride substrate (a, n, d)[a]	Coupling partner	Solvent/base	Temperature (°C)	Time (h)	Product	Yield (%)	Reference
1	$[Pd(dba)_2]$ + 1.25 **75**(2)	(n) 		THF/NaO^{t}Bu	70	12		80	[103]
2	$Pd(OAc)_2$ + 1.25P^{t}Bu$_3$(2)	(d) 	”	”	”	”		91	[103]
3	$[Pd(dba)_2]$ + 1.25 **75**(2)	(n) 		”	100	”		78	[103]
4	$Pd(OAc)_2$ + PCy_3(5)		–	Dioxane/NaO^{t}Bu	70	3		93	[105]
5	$[Pd(dba)_2]$ + **76**(1)	(n) 		Toluene/NaN(SiMe$_3$)$_2$	r.t.	12		71	[107]
6	$Pd(OAc)_2$ + 2 **33**(0.1)	(d) 		Toluene/NaO^{t}Bu	70	24		74[b]	[108]

7	$[Pd_2(dba)_3]$ + 2 **77**(2)	(a) 	$^{n}PrNO_2$	DME/Cs_2CO_3	60	Not specified		86	[110]
8	$[Pd_2(dba)_3]$+ 2 **78**(3)	(d) 		Toluene/$LiN(SiMe_3)_2$	80	1		87	[109]
9	$[Pd(dba)_2]$ + **57**	(n) 		Pyridine/NaH	85	14		73	[111]

[a] a: activated, n: non-activated, d: deactivated (with respect to oxidative addition).
[b] Ratio of mono- vs. diarylated product 7:1.

Table 10
Selected Buchwald–Hartwig amination reactions with aryl chloride substrates

Entry	Catalyst	Catalyst loading (mol% Pd)	Chloride substrate (a, n, d)[a]	Amine	Solvent/base	Temperature (°C)	Time (h)	Conversion {isolated yield} (%)	Reference
1	**79**	2.0	(n) 		Toluene/NaO^{t}Bu	120	6	81	[113]
2	”	”	(n) 		”	”	6	60	[113]
3	$Pd(OAc)_2$ + **80**	1.0	(n) 		”	85	12	{92}	[114]
4	$Pd(OAc)_2$ + **75**	”	”		”	100	”	{85}	[114]
5	$[Pd(dba)_2]$ + 2 **43**	”	(d) 	$HNBu_2$	”	”	20	{93}	[66]
6	”	”	”		”	70	15	{95}	[66]
7	$Pd(OAc)_2$ + 2 **43**	2.0	”	H_2N-*n*-hex	”	”	18	{92}	[66]
8	$Pd(OAc)_2$ + 2 **34a**	1.0	(n) 		”	r.t.	19	{98}	[117]
9	”	2.0	”	$HNBu_2$	”	”	18	{81}	[117]
10	$[Pd_2(dba)_3]$ + 4 **34a**	4.0			”	80	20	{73}[b]	[117]
11	$[Pd_2(dba)_3]$ + 2 **83**	1.0	(n) 		^{t}BuOH/KOH	100	3	{78}	[118]
12	”	1.0	”		^{t}BuOH/K_2CO_3	”	19	{87}[c]	[118]

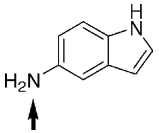
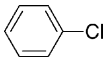
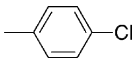
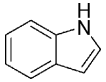
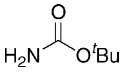
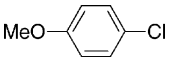
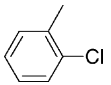
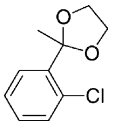
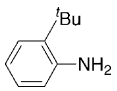
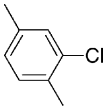
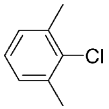
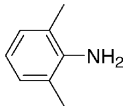
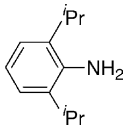
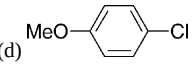
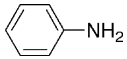
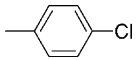
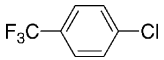
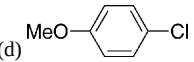
13	$[Pd_2(dba)_3]$ + 2.5 **83**	2.0	”		”	110	3	{80}[d]	[118]
14	$Pd(dba)_2$ + 0.8P^{t}Bu$_3$	5.0	(n) 	H_2NPh	”	r.t.	25	{75}	[121]
15	”	”	(n) 		Toluene/Cs_2CO_3	100	12	{64}	[121]
16	$Pd(dba)_2$ + 2P^{t}Bu$_3$	4.0	”		Toluene/NaOPh	100	24	{59}	[121]
17	**84a**	1.0	(d) 	$HNBu_2$	THF/NaO^{t}Bu	r.t.	0.25	{87}	[122]
18	**84b**		(n) 		”	”	”	{84}	[122]
19	$Pd(dba)_2$ + 3 **39a**	2.0			Toluene/NaO^{t}Bu	105	2	{89}	[123]
20	”	”	(n) 	H_2NOct	”	”	1	{92}	[123]
21	$Pd(OAc)_2$ + 2 **85**	0.5			”	120	20	{96}[b]	[124]

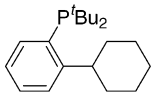
Table 10 (*Continued*)

Entry	Catalyst	Catalyst loading (mol% Pd)	Chloride substrate (a, n, d)[a]	Amine	Solvent/base	Temperature (°C)	Time (h)	Conversion {isolated yield} (%)	Reference
22	”	”	”		”	”	”	{70}[b]	[124]
23	[$Pd_2(dba)_3$] + 2 **53**	4.0	(d) 		”	80	Not specified	{89}	[125]
24	[$Pd_2(dba)_3$] + 2 **24**	2.0	”		Dioxane/KO^{t}Bu	100	3-24 (not specified)	{91}	[129]
25	”	”	”	$HNBu_2$	”	”	3-24 (not specified)	{98}	[129]
26	[$Pd_2(dba)_3$] + **87**	4.0	(n) 		Dioxane/NaO^{t}Bu	110	30	{66}	[131]
27	**1a** + LiBr	0.1	(a) 		Toluene/KO^{t}Bu	135	24	98	[135]
28	**92**	1.0	(d) 		Dioxane/NaO^{t}Bu	70	0.5	{100}	[137]
29	**10** + 2P^tBu_3	0.1	”	”	Toluene/NaO^{t}Bu	100	17	{96}	[138]

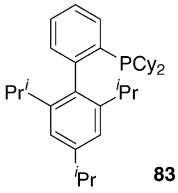
[a] a: activated, n: non-activated, d: deactivated (with respect to oxidative addition).
[b] Product: (Ar)(Ar′)NH.
[c] >20:1 selectivity for indicated NH.
[d] 8:1 selectivity for indicated NH. Product contains some of the *meta* isomer (ratio 13:1).

dissociation from their Pd(0) bis-chelate complexes, which appears to be a prerequisite for oxidative addition of the aryl chloride. Subsequently Hartwig and co-workers demonstrated that the bulky ferrocenyl mono-phosphine **43** shows very general activity in a wide range of amination of aryl chlorides substrates with both primary and secondary amines, although, as is often the case, lower activity is seen in the coupling of *ortho*-substituted aryl halides with non-cyclic secondary alkyl amines (e.g. entries 5–7) [66]. Particularly interesting is the high activity and selectivity for mono-arylation observed in the coupling of unhindered aryl chlorides with unhindered primary alkylamines (e.g. entry 7). Such reactions are difficult for two reasons, firstly selectivity for mono-over diarylation can be low with small substrates and secondly, monophosphine-containing catalysts often give large amounts of hydrodehalogenation products in this class of reaction.

Buchwald and co-workers have performed extensive studies on the use of *ortho*-biphenyl-containing phosphines in the amination of aryl chlorides [115–117]. The bulky ligand **34a** proves to be particularly effective for the room temperature coupling of several aryl chlorides (e.g. entries 8 and 9), though increasing the temperature substantially broadens the scope of the reaction, for instance to the use of hindered substrates (entry 10). The Pd/**34a** system gives high selectivity for the mono-arylation of primary alkylamines with unhindered aryl chlorides. The use of the milder base K_3PO_4 and the smaller ligands **33** or **34b** allows aryl chlorides with base-sensitive functionalities such as enolizable ketones, methyl esters, nitriles and nitro groups to be coupled. Further evidence for the putative participation of π-coordination of the secondary aryl ring of the *ortho*-biphenyl moiety in catalysis (see Section 3.2 above) is provided by the observation that when the partially saturated ligand **82** is used, then significantly lower activity results in room temperature aminations.



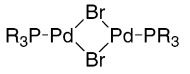
82



83

Recent work in the Buchwald group on the extension of amination of aryl sulfonates led to the development of the new, sterically hindered ligand **83** which allows transformations that are either difficult or not possible using other catalysts [118]. For instance aryl chlorides can be coupled to anilines containing unprotected carboxylic acid residues (entry 11). The Pd/**83** system often gives results which are complementary to copper-based catalysis. Thus, aryl chlorides couple selectively with the amine residues of aminobenzamides and aminoindoles (entries 12 and 13), while aryl iodides are coupled using Cu-containing systems to the amido and indole nitrogens, respectively.

Tri-*tert*-butylphosphine complexes have again proved to be active in aryl chloride activation, originally by Nishiyama and co-workers [119,120]. Hartwig and co-workers found these catalysts to be particularly effective for amination under mild conditions (e.g., entry 14) [121]. The Pd/P^{t}Bu$_3$ catalyst system also allowed an extension of the reaction to the amination of aryl chlorides by both azoles and carbamates (e.g. entries 15 and 16, respectively). In these cases, the choice of base proves to be crucial with Cs_2CO_3 and sodium phenoxide giving optimum conversions with azoles and carbamates respectively. Changing from a 'classical' Pd(0) or Pd(II) precursor to the preformed dimeric Pd(I) complexes **84** leads to a substantial rate enhancement, with high conversions to coupled product obtained within 15 min at room temperature (e.g. entries 17 and 18) [122]. The short reaction times allow greater functional group tolerance. For instance the nitro group, which is typically unstable in the presence of sodium *tert*-butoxide, is coupled with ease using this base.

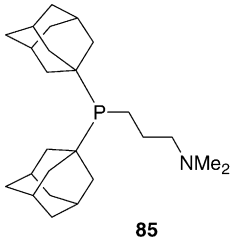


84a: PR$_3$ = P^{t}Bu$_3$
b: PR$_3$ = P^{t}Bu$_2$(1-Ad)

Guram and co-workers examined the use of phenyl backbone-derived P,O- and P,N-ligands in the amination of aryl chlorides [123]. Of those tested, a catalyst containing the P,O-ligand **39a** proved to be most active and can be used in the coupling of non-activated aryl chlorides with a wide range of amines (e.g. entries 19 and 20). All the reactions reported are complete within 1–3 h at a temperature of 105 °C.

Beller and co-workers applied the butyldiadamantylphosphine ligand **14** and the related phosphine, **85**, in aryl chloride aminations and found them to be particularly useful for the coupling of very sterically hindered substrates (e.g. entries 21 and 22) [124]. These ligands tend to show improved performance compared with P^{t}Bu$_3$, PCy$_3$ and PCy$_2$(*o*-biphenyl) (**34b**), as well as several other non-typical phosphines for chloride amination.

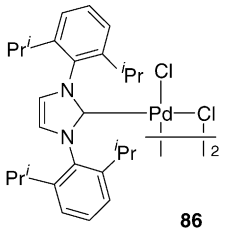
Although it has to be used in somewhat higher loadings than comparable trialkylphosphines, the bicyclic aminophosphine **53** can be used to couple electron poor and rich aryl chlorides with anilines and primary and secondary alkylamines (e.g. entry 23) [125]. This is despite the fact that triaminophosphine ligands are typically much poorer σ-donors than trialkylphosphines [126,127]. Verkade argued that the higher than expected activity is due to the fact that the constrained geometry of the bicyclic amine, coupled with possible N → P transannulation may give enhanced electron-donating abilities, compared with simple triaminophosphines, which accelerates oxidative addition. Further the high bulk of the ligand would facilitate reductive elimination.



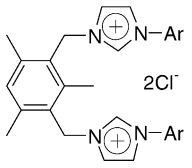
85

5.2. Carbenes

N-Heterocyclic carbene complexes have once again been found to be good catalysts for the amination of aryl chlorides. Nolan and co-workers screened several carbene complexes derived *in situ* from *N*,*N*′-diaryl-sustituted imidazolium salts and found that the bulky salt **24** gave the best activity [128,129]. This system was found to be effective with a range of electron rich and poor aryl chlorides coupled with primary, secondary, cyclic and acyclic amines (e.g. entries 24 and 25). Subsequently, Nolan found that the preformed complex **86** is sufficiently air and moisture stable that reactions can be performed under air using undried, reagent grade solvents, making this system particularly attractive in the synthetic laboratory [130]. Meanwhile, Cheng and Trudell have shown that the potentially chelating bis-carbene system formed *in situ* from the bis-imidazolium salt **87** can be used for the synthesis of *N*-aryl- and -heteroaryl-substituted 7-azabicyclo[2.2.1]heptanes (eg. entry 26) [131].

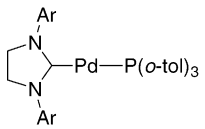


86

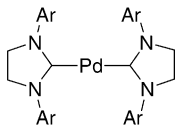


87: Ar = C_6H_2-2,4,6-^{i}Pr$_3$

The assumption that carbene ligands form strong, non-labile complexes in catalytic coupling reactions has been challenged by Caddick and Cloke, who have investigated the use of preformed carbene complexes as catalysts in amination reactions [132,133]. They showed that catalyst **61b** can be used to couple 4-chlorotoluene with morpholine and piperidine [132], but that much better activity is obtained if the mixed phosphine/saturated carbene complex **88** is used in its place; the lability of phosphine probably facilitates oxidative addition [133]. Surprisingly, the bis-carbene complex **89** shows very similar activity, implying that the carbene ligands may also be labile. Evidence for this was provided by ligand exchange reactions which showed that phosphine–carbene ligand exchange is facile under mild conditions at Pd(0) centres. Subsequent detailed work on the oxidative addition of aryl chlorides to Pd(0) bis-carbene complexes indicates that this proceeds via a dissociative mechanism generating a mono-carbene species and that the dissociation step is rate-determining [134].



88



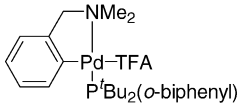
89

Ar = C_6H_3-2,6-^{i}Pr$_2$

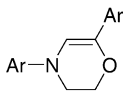
5.3. Palladacycles and their adducts

Palladacyclic complexes have also been investigated as catalysts for the amination of aryl chloride substrates. Beller showed that the complex **1a** can be used to couple activated aryl chlorides (e.g. entry 27) [135]. The use of potassium *tert*-butoxide as base is essential since no reaction is observed with the sodium salt. The presence of some of the *meta* isomer in the product indicates that the use of KO^{t}Bu leads to the formation of some benzyne which is subsequently aminated in a Pd-free pathway [136].

We investigated the use of the phosphine adducts **65a**, **65**, **66** and **90** (formed *in situ*) in the coupling of 4-chloroanisole with morpholine and compared the results with the catalysts formed *in situ* from the phosphine ligands and palladium acetate [84]. When palladium acetate is used as the palladium source the order of the activity of the ligands is PCy_2(*o*-biphenyl) > P^{t}Bu$_2$(*o*-biphenyl) > PCy_3 > P^{t}Bu$_3$. Changing to the palladacyclic precursors leads to an increase in activity of between 2.5- and 6-fold, except with PCy_3 which shows no improvement. The best phosphine proves to be P^{t}Bu$_3$ under these conditions. These results are in contrast with those found in the Suzuki coupling, where the PCy_3 shows the maximum enhancement on changing palladium precursor, while very little change is observed with P^{t}Bu$_3$(see Section 3.4 above).



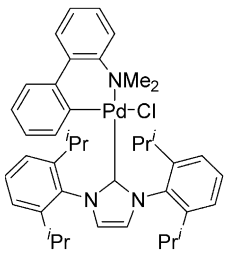
90



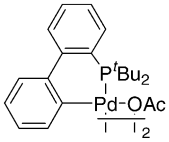
91

An interesting side reaction was shown to occur in all of these amination reactions, regardless of catalyst, namely the formation of 4,6-diarylated-3,4-2*H*-[1,4]oxazines, **91**. The formation of these compounds requires three distinct catalytic processes: amination, oxidative formation of the double bond and a subsequent Heck coupling.

Nolan and co-workers have examined the use of the preformed carbene adduct **92** and found that it gives good activity in a range of amination reactions with activated and deactivated substrates at 70 °C in less than 4 h (e.g. entry 28) [137]. Increasing the temperature (110 °C) and decreasing the catalyst loading (0.05 mol% Pd) gives a TON of 460 (23% conversion).



92



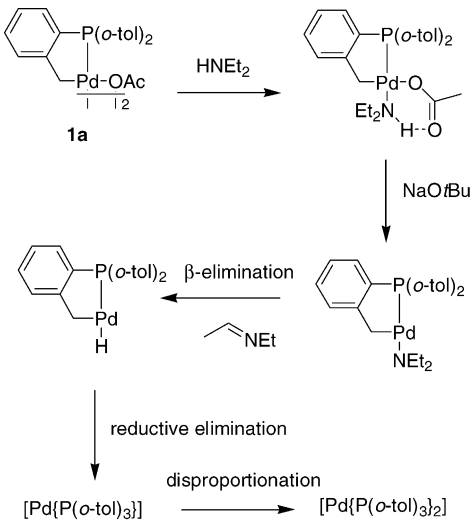
93

Subsequently, we demonstrated that *in situ* generated tricyclohexylphosphine and, in particular, tri-*tert*-

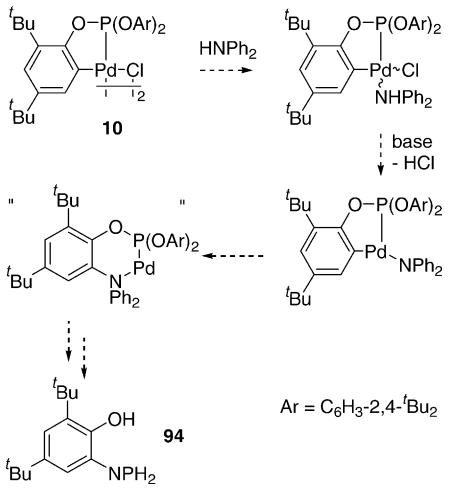
butylphosphine adducts of the phosphite- and phosphinite-based palladacycles **10** and **71** can be used to good effect in the coupling of activated to deactivated aryl chlorides with secondary aromatic and aliphatic amines (e.g. entry 29) [138]. Here a maximum TON of 960 (96% yield) is observed in the coupling of the deactivated susbtrate 4-chloroanisole at 100 °C.

Zim and Buchwald have recently shown that the palladacycle **93**, formed by the reaction of palladium acetate with the phosphine ligand **34a**, is a convenient air-stable replacement for systems formed *in situ* from the parent ligand [139]. In this case, it was noted that when anilines are used as substrates it is necessary to add triethylamine to the reaction mixture, otherwise no reaction is observed. The authors speculated that the amine is necessary to act as a reducing agent to generate Pd(0) via β-elimination. Such a reductive mechanism was previously proposed by Hartwig, who showed that the palladacycle 1a can undergo a reduction in the presence of diethylamine to generate [Pd{P(*o*-tolyl)$_3$}$_2$] as an active catalyst in amination reactions. (Scheme 18) [140].

By contrast we find that the palladacyclic catalysts formed *in situ* from P^{t}Bu$_3$ and the complexes **10** and **71** are perfectly capable of catalysing the coupling of anilines that are not able to undergo β-elimination reactions, indicating that in these cases there must be at least one other reductive activation pathway operative [138]. Tentative evidence is provided by a peak in a GC–MS spectrum of a reaction between complex **10** and diphenylamine in the presence of sodium *tert*-butoxide, which shows a mass and fragmentation pattern consistent with the formation of the *ortho*-aminated phenol **94**. An activation mechanism that may account for the presence of this compound is shown in Scheme 19, this is essentially a 'stoichiometric amination' of the orthometallated ligand.



Scheme 18. The activation of a palladacyclic catalyst *via* β-elimination from an amide ligand.



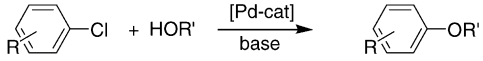
Scheme 19. Putative activation of a palladacycle by 'stoichiometric amination'.

6. Catalysts for the etherification of aryl chlorides

The catalytic etherification of aryl chlorides (Scheme 20) has not been investigated as extensively as the related amination reaction described above.

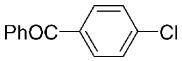
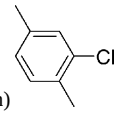
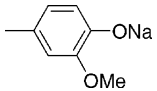
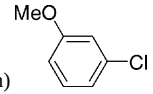
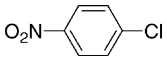
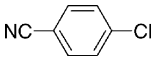
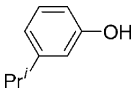
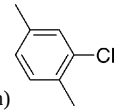
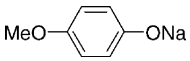
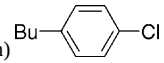
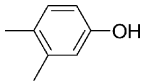
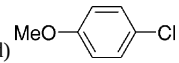
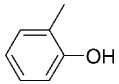
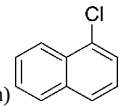
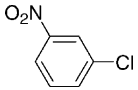
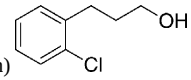
Mann and Hartwig showed that palladium complexes of the ligand 1,1′-bis(diphenylphosphino)ferrocene, dppf, can be used to couple activated aryl chlorides (e.g. Table 11, entry 1) [141]. When the ferrocenyl bis-phosphine ligand is replaced by either the bulky ferrocenyl monophosphine ligand **13** or P^{t}Bu$_3$ then the reaction can be extended to more electron-rich aryl chlorides with both alkoxides and aryloxides (entries 2 and 3) [142]. Watanabe and co-workers also demonstrated the utility of Pd/P^{t}Bu$_3$ systems in the formation of *tert*-butyl ethers from aryl chlorides [143]. Interestingly, Hartwig and co-workers found that the ligand in the active form of the catalyst system derived from Pd/**13** is not **13** but rather the pentaphenylated ligand **43**, formed by an *in situ* catalytic phenylation process [144]! When catalysts containing the preformed ligand **43** are used then reactions can be performed under considerably milder conditions (e.g. entries 4 and 5). The likely increase in the rate of reaction is presumably due to the increased rate of reductive elimination, a difficult process for palladium alkoxides and aryloxides and almost certainly the rate-determining step in most etherification reactions.

At about the same time as Hartwig's group was investigating the use of ferrocenyl-based ligands and P^{t}Bu$_3$ in etherification reactions, the Buchwald group was focussing on the use of bulky, electron-rich aryldialkylphosphines. In particular, the *o*-biphenyl-containing ligand **34a** proved to be



Scheme 20. Catalytic etherification of aryl chlorides, R′: alkyl, aryl.

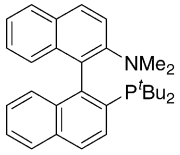
Table 11
Selected catalytic etherification and thioetherification reactions with aryl chloride substrates

Entry	Catalyst	Catalyst loading (mol% Pd)	Chloride substrate (a, n, d)[a]	Alcohol/alkoxide	Solvent/base	Temperature (°C)	Time (h)	Yield (%)	Reference
1	$Pd(OAc)_2$ + 2dppf	10.0	(a) 	NaO^tBu	Toluene	95	12	89	[141]
2	$[Pd(dba)_2]$ + P^tBu_3	5.0	(n) 		”	110	24	81	[142]
3	$[Pd(dba)_2]$ + **13**	2-5 (not specified)	”	NaO^tBu	”	85	12	71[b]	[142]
4	$[Pd(dba)_2]$ + **43**	5.0	(n) 	”	”	80	6	92	[144]
5	”	5.0	(a) 	”	”	r.t.	5	93	[144]
6	$Pd(OAc)_2$ + 1.5 **34a**	2.0	(a) 		Toluene/K_3PO_4	100	14–24 (not specified)	91	[145]
7	$[Pd_2(dba)_3]$ + 1.5 **95**	2.0	(n) 		Toluene	110	14–26 (not specified)	92	[145]
8	$Pd(OAc)_2$ + 1.5 **96**	2.0	(n) 		Toluene/NaH	100	14–26 (not specified)	76	[145]
9	$Pd(OAc)_2$ + 1.5 **97**	2.0	(d) 		Toluene/K_3PO_4	”	14–26 (not specified)	73	[145]
10	$Pd(OAc)_2$ + 1.25 **98**	2.0	(n) 	^nBuOH	Toluene/Cs_2CO_3	23	21.5	88	[146]
11	$Pd(OAc)_2$ + 1.25 **95**	2.0	(a) 	”	”	70	14	94	[146]
12	$Pd(OAc)_2$ + **98**	2.0	(n) 	–	”	65	21	85	[148]

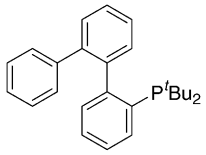
[a] a: activated, n: non-activated, d: deactivated (with respect to oxidative addition).
[b] Free phenol isolated after hydrolysis with CF_3CO_2H/CF_3SO_3H.

effective for the coupling of activated aryl chlorides (e.g. entry 6) [145]. Optimisation studies showed that the use of K_3PO_4 as a base often obviates the need to pre-form an aryloxide salt. *Ortho*-substituted non-activated aryl chlorides are better etherified by catalysts containing the binaphthyl ligand **95** (e.g. entry 7). While certain non-activated aryl chlorides which lack *ortho*-substituents can be activated using the modified ligand **96** (e.g. entry 8), small, deactivated chlorides such as 4-chloroanisole require the use of the diadamantylphosphine-containing ligand **97** (entry 9).

Alcohols with β-hydrogens are typically difficult to couple since β-elimination competes with the slow C–O reductive elimination step, leading to the predominant formation of the arene derived from the aryl halide by hydrodehalogenation. Buchwald and co-workers found that the use of ligand **98** facilitates the coupling of β-hydrogen-containing alcohols with the bulky chloride 2-chloro-*meta*-xylene and 1-chloronaphthalenes with good selectivity (e.g. entry 10), but smaller chlorides could not be used successfully. By contrast the dimethylamino-containing ligand **95** allowed the coupling of a range of smaller *ortho*- and *meta*-substituted aryl chlorides (e.g., entry 11). The ligand **98** also proves to be useful for the synthesis of cyclic ethers *via* intramolecular C–O bond formation (e.g. entry 12), again the success of the reaction relies on the suppression of competitive β-elimination [147,148].



95



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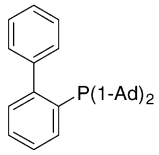
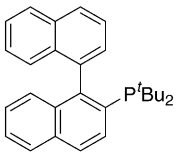


97



98

7. Conclusions

In summary, it can be seen that the drive to produce catalysts that are able to activate aryl chlorides has reaped many rewards. Not only activated and non-activated but also deactivated chlorides can be readily coupled in a range of reactions. In many cases, it is possible to push the catalyst systems further to allow reactions to be performed under increasingly mild conditions and/or lower catalyst loadings — advances in both these areas substantially increase the attractiveness of aryl chloride substrates over their bromide or iodide counterparts.

It is apparent that no one class of ligands or catalysts acts as a panacea for all reactions types, indeed optimisation for one reaction may lead to poor activity in other transformations Despite this some ligands do show a comparatively broad range of utility, these include bulky trialkylphosphines such as P^tBu_3 and, to a lesser extent, PCy_3. Handling problems associated with the former's air-sensitivity can be circumvented by the use of the air-stable phosphonium salts or sometimes by the use of the preformed complex $[Pd(P^tBu_3)_2]$. The phosphines containing *o*-biphenyl residues introduced by Buchwald also display a very broad scope in coupling reactions, although their use has not yet been reported in Heck reactions. *N*-Heterocyclic carbenes are proving to be useful, although their reactivity with electronically deactivated aryl chlorides can sometimes be limited.

It is also apparent that care is needed in selecting the right palladium source. While palladium acetate or palladium dibenzylideneacetone complexes remain the most commonly used precursors, they do not always give optimum performance. Palladacyclic precursors, for instance, can often give much higher activity when used in combination with the same ligands. This is particularly true for tricyclohexylphosphine whose utility in a given reaction can be highly susceptible to palladium source.

Further, as these reactions are taken up in large scale syntheses then issues of catalyst loading, stability and longevity will become increasingly important. To this end, it is likely that the future design of many catalyst systems will focus on the stabilisation of the catalyst resting state in order to increase longevity by retarding the rate of precipitation of bulk palladium.

Another area that is likely to evoke a lot of interest in future research is the issue of 'tuneable' catalyst selectivity. Fu has already demonstrated that aryl chlorides can be activated in preference to aryl triflates while Buchwald has shown that different NH functions in the same molecule can be arylated with different catalyst systems.

In conclusion while the activation of aryl chlorides is now viable, there are still plenty of interesting problems and taxing issues to be tackled in the use of this class of substrates in coupling chemistry.

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