

Palladacyclic catalysts in C–C and C–heteroatom bond-forming reactions

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Palladacycles are amongst the most active catalysts in Heck-type carbon–carbon bond formation and related carbon–heteroatom bond forming reactions. For instance they have recently emerged as showing the highest activity in the Suzuki coupling of electronically challenging aryl chloride substrates. In addition to the high activity they display, their ease of synthesis, facile modification and comparative stability all act to enhance their appeal.

Introduction

In the last decade the reputation of palladacyclic catalysts has swung from them being viewed as deactivation products through to the realisation that they are amongst the most active catalysts for C–C and C–heteroatom bond formation. The aim of this review is to chart this change in their fortune.¹ Here we will be concentrating on preformed palladacycles acting as pre-catalysts rather than catalysis that proceeds *via* the formation of a palladacyclic intermediate, another highly topical area of research.²

What do we mean by palladacycles? The general structures of the complexes we will be concentrating on are shown in Fig. 1

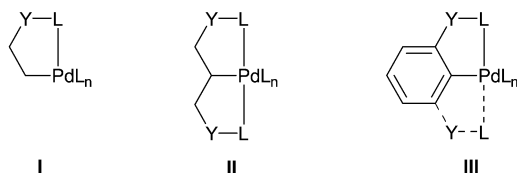


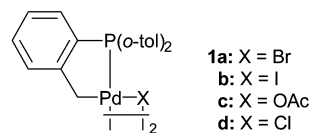
Fig. 1 Generalised palladacyclic structures. L = donor, Y = linker group.

and fall into two general classes: the first are simple palladacycles (I) where one ligand coordinates to the palladium centre in a κ^2 -L,C manner (L = donor) to form a stable, five membered chelate; the second are so called ‘pincer’ complexes (II) where the metallated carbon is supported by two donor groups in a κ^3 -L,C,L fashion. The donor groups ‘L’ are typically PR_2 , NR , NR_2 or SR and there is usually some degree of unsaturation between

Robin Bedford was born in 1969 in Kent and spent most of his formative years in Somerset, where he received his early education. He studied for a BSc degree in biochemistry at the University of Sussex between 1988 and 1991. His D.Phil. research was performed at Sussex between 1991 and 1994 under the supervision of Dr Penny Chaloner. From there he went to Imperial College of Science Technology and Medicine as a post-doctoral research associate, working with Professor Anthony Hill. He gained his first academic appointment at Trinity College Dublin in 1996 from where he moved to his current position as lecturer in inorganic chemistry at the University of Exeter in 1998.

the metallated C and the donor group ‘L’. In nearly all the cases in this article the carbon donor is an orthometallated aryl ring (structure III).

The study of palladacyclic catalysts, and indeed metallacyclic catalysts in general, has almost certainly been hampered by the misconception that such species are likely to be deactivation products and that the carbo-metallation renders them catalytically inactive. This is illustrated by the fact that complexes **1a** and **b**, examples of the most widely studied class of palladacyclic pre-catalysts which show high activity in a range of coupling reactions,^{1b} were essentially dismissed as deactivation products, over a decade before their renaissance, by Heck who observed their formation in the coupling of dienes with aryl halides.³



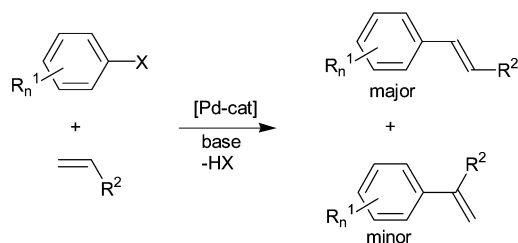
Perhaps the earliest demonstration that palladacyclic catalysts could show higher activity than their non-metallated analogues was in the hydrogenation of alkenes and alkynes reported by Lewis.⁴ He found that the orthometallated complex $[\text{PdCl}\{\kappa^2\text{-}P,C\text{-}P(\text{OC}_6\text{H}_4)(\text{OPh})_2\}\{\text{P}(\text{OPh})_3\}]$ formed by thermolysis of $[\text{PdCl}_2\{\text{P}(\text{OPh})_3\}_2]$ could be used as an active pre-catalyst while the precursor complex is completely inactive. This enhancement in activity on orthometallation was not only observed for palladium, but also for complexes of rhodium, ruthenium and cobalt. Since then by far the greatest application of palladacyclic catalysts has been in C–C coupling and, to a lesser extent, C–heteroatom coupling. It is this area to which the rest of this discussion will be dedicated.

Initially we will focus on the development of catalysts of the general classes I and II. The earlier work in this field tended to be incremental and empirical and catalysis was typically limited to ‘easier’ to couple substrates such as aryl iodides and bromides. Later we will address how the catalysts have been modified to confer very high activity in the coupling reactions of far more challenging aryl chloride substrates. Studies on the (lack of) recyclability of these catalyst types helped spark more in-depth examinations of what makes this class of catalyst so active and the results from these studies will be summarised at the end of the article.

Catalysis of C–C and C–heteroatom bond formation

P,C-Palladacyclic catalysts

The field was initiated in 1995 by Herrmann and co-workers when they reported that the complex **1c** and related species showed by far the highest activity in the Heck coupling of aryl halides with simple alkenes (Scheme 1) then reported.⁵ These

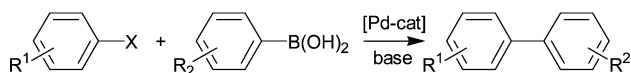


Scheme 1 The Heck coupling of aryl halides with alkenes.

catalysts are readily synthesised by the reaction of the appropriate 2-methyl substituted aryl phosphines with a palladium(II) salt such as palladium acetate. Indeed thermal reaction of a simple palladium(II) precursor with the ligand to be carbometallated is typical for the synthesis of nearly all of the catalysts discussed here.

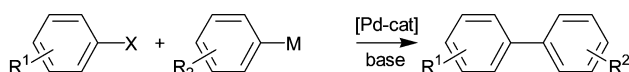
For the first time turn-over numbers (TONs)⁶ of up to 1 000 000 were observed in the Heck coupling of *n*-butylacrylate with the electronically activated (electron-deficient) aryl bromide, 4-bromoacetophenone. Later it was realised that this particular bromide is not an especially good indicator of catalyst activity, since palladium acetate in the absence of any additional co-ligands shows TONs of up to 100 000 in coupling reactions with this substrate.⁷ With the more electronically challenging (electron-rich) bromide, 4-bromoanisole, the maximum TON achieved was somewhat lower at 630. A particularly interesting observation is that the catalyst **1c** can be used to couple aryl chlorides, albeit electronically activated examples such as 4-chloroacetophenone. This class of substrates is particularly relevant from an industrial point of view as they are generally cheaper and more widely available than their bromide or iodide counterparts. This topic will be discussed in detail later. The performance with aryl chlorides can be enhanced by the use of appropriate additives such as [NBu₄]Br or [PPh₄]Cl.^{1b} The latter salt even facilitates the use of the electronically deactivated substrate, 4-chloroanisole, with TONs of up to 190 achieved. As well as being useful for the coupling of simple alkenes, catalysts of the type **1** can be used with more challenging substrates, for instance in the formation of tri-substituted alkenes.⁸

The application of catalysts of the type **1** to coupling reactions is not limited to the Heck reaction; Beller demonstrated that **1c** could be used to good effect in the Suzuki biaryl coupling reaction (Scheme 2). Thus TONs of up to 74 000,



Scheme 2 The Suzuki coupling reaction of aryl halides.

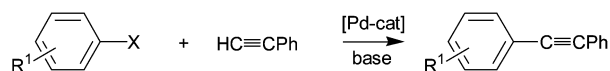
7 600 and 2 100 are seen in the coupling of phenylboronic acid with 4-bromoacetophenone, 4-bromoanisole and 4-chloroacetophenone respectively.⁹ Complex **1c** can also be used in the Stille coupling (Scheme 4) of aryl bromide substrates,^{10,1b} as well as the related coupling of aryl Grignard or zinc reagents (the Kumada and Negishi reactions, Scheme 3).^{1b} It can also be used



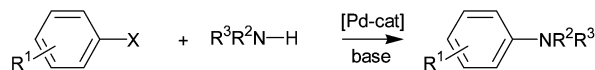
Scheme 3 The Stille (M = SnR₃), Kumada (M = MgX) and Negishi (M = ZnX) coupling reactions.

in the Sonogashira coupling of aryl bromides with phenylacetylene (Scheme 4)^{1b} and the Buchwald–Hartwig amination of aryl bromides and chlorides (Scheme 5).¹

As well as the good activity it shows, there are several other advantages associated with the use of the preformed catalyst **1c** over catalysts formed *in situ* from tri(*o*-tolyl)phosphine and palladium acetate, such as its air-stability, ease of handling and



Scheme 4 The Sonogashira reaction.

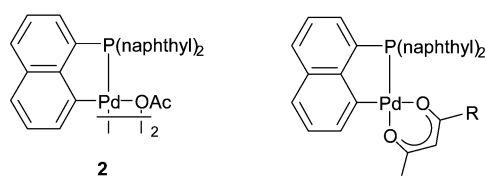


Scheme 5 The Buchwald–Hartwig amination reaction.

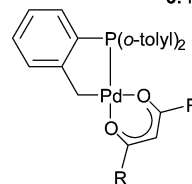
the fact that the phosphine : palladium ratio can be maintained at 1 : 1.

While complexes of the type **1** were the first, and by far the most widely studied phosphorus-based palladacyclic catalysts in coupling reactions, they are by no means the only ones.¹¹ Shaw and co-workers demonstrated that the palladated naphthyl complexes **2** and **3** and the modified versions of Herrmann's system, **4**, can also be employed. These catalysts give TONs of up to 1.12 million in the Heck coupling of methyl acrylate with iodobenzene after 13 days at 95 °C.¹²

We synthesised the orthometallated triarylphosphite complex **5a**, as a mixture of *cis* and *trans*-isomers, by reaction of palladium dichloride with the very inexpensive ligand tris(2,4-di-*tert*-butylphenyl)phosphite, **6**.¹³ Complex **5a** shows what was then the highest activity in the Suzuki coupling of aryl bromides, with TONs of up to 1 million in the coupling of 4-bromoacetophenone with phenylboronic acid. With the more electronically challenging substrate, 4-bromoanisole, then the maximum TON obtained in the coupling with phenylboronic acid is 30 000. Complex **5a** is also an active catalyst for the Stille coupling of phenyltributyltin with aryl bromides, showing TONs of up to 830 000 with 4-bromoacetophenone, but only 840 with 4-bromoanisole. The catalyst is also highly active in the Heck coupling of aryl bromides with simple alkenes.¹⁴ Thus TONs of up to 5.75 million are seen in the coupling of 4-bromoacetophenone and styrene and up to 9 800 in the coupling of 4-bromoanisole with *n*-butylacrylate. By contrast, substantially lower activity is seen when the triphenylphosphine adduct **7** is employed.

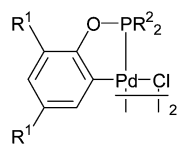


3: R = Me, CF₃



4: R = Me, CF₃

It is interesting to note that the high activity noted with complex **5a** is despite the fact that the π -acidic, orthometallated ligand renders the palladium centre electron deficient with respect to the palladacyclic phosphine systems described above. At the time of this research it was more or less assumed that oxidative addition of the aryl bromide would be rate limiting. If this was indeed the case then triarylphosphites should be relatively poor ligands. At the same time, Beller demonstrated that catalysts formed *in situ* from palladium acetate and the ligand **6**, could even be used to couple activated and non-activated aryl chlorides in both Heck and Suzuki reactions, a topic that will be addressed further later.^{15,16} Therefore we were

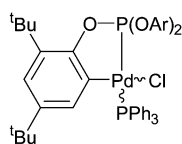


5a: $R^1 = {}^t\text{Bu}$; $R^2 = \text{OC}_6\text{H}_3\text{-2,4-}{}^t\text{Bu}_2$

b: $R^1 = \text{H}$; $R^2 = \text{Ph}$

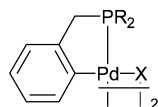
c: $R^1 = {}^t\text{Bu}$; $R^2 = \text{Ph}$

d: $R^1 = {}^t\text{Bu}$, $R^2 = {}^i\text{Pr}$



7: $\text{Ar} = \text{C}_6\text{H}_3\text{-2,4-}{}^t\text{Bu}_2$

interested to see what effect varying the steric and electronic properties of complexes of the general type **5** would have on Suzuki coupling reactions and we synthesised the analogues of **5a**, complexes **5b–d**.¹⁷ The size of the substituents on the orthometallated ring is important with **5b** showing significantly lower activity than the bulky analogue **5c**. However **5b** is still far more active than the bulky phosphite complex **5a**, showing TONs of up to 290 000 in the Suzuki coupling of the electronically deactivated substrate 4-bromoanisole with phenylboronic acid – nearly ten times higher than that shown by **5a**. This indicates that increasing the electron density on the palladium leads to greater activity, since the orthometallated phosphinite ligand in **5b** is less π -acidic than that of **5a**. Increasing the steric bulk leads to a vast improvement in activity with **5c** giving a TON of 2.6 million in the same reaction. The introduction of ${}^i\text{Pr}$ groups onto the phosphorus of the phosphinite ligand instead of phenyl groups leads to a further increase in activity with a TON of 4.2 million observed, again indicating that a reduction in π -acidity is beneficial. When an extra equivalent of ligand is added to the palladacyclic phosphinite complexes then even greater activity results. Thus TONs of up to 8.75 million are seen with **5c** and when **5d** is employed in the coupling of phenylboronic acid with the activated substrate, 4-bromoacetophenone, then a huge TON of 475 million is obtained. It seems that *increasing* the electron density on the palladium when using π -acidic phosphite or phosphinite-based palladacycles increases the catalytic activity; however it is important to strike the right electronic balance. This is demonstrated by the fact that the complex **8a**, which is sterically essentially identical to **5b**, but is more electron rich at the palladium centre, shows less than half the TON in the coupling of phenylboronic acid with 4-bromoanisole.¹⁸ The electronic picture is complicated further by the observation that this result is highly dependent on palladium source: there is not a particularly large difference in activity between the catalysts formed *in situ* from $[\text{Pd}(\text{dba})_2]$ and either $\text{Ph}_2\text{P}(\text{CH}_2\text{Ph})$ or $\text{Ph}_2\text{P}(\text{OPh})$ and the performances of $[\text{PdCl}_2\{\text{PPh}_2(\text{CH}_2\text{Ph})\}_2]$ and $[\text{PdCl}_2\{\text{PPh}_2(\text{CH}_2\text{Ph})\}_2]$ are again very similar.¹⁸



8a: $R = \text{Ph}$; $X = \text{Cl}$

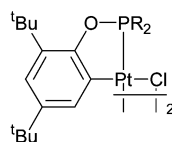
b: $R = \text{Ph}$; $X = \text{Br}$

c: $R = {}^t\text{Bu}$; $X = \text{Br}$

Buoyed up by the results obtained with the complexes **5** in the Suzuki coupling of deactivated aryl bromides, we then tried coupling the deactivated aryl chloride, 4-chloroanisole using the most electron-rich of the catalysts, complex **5d**, but obtained very poor results with only 6 turn-overs observed. Since then we have found that this catalyst will catalyse the coupling of non-activated and activated aryl chlorides with conversions of 76% and 100% respectively in the coupling of phenylboronic acid with 4-chlorotoluene and 4-chlorobenzaldehyde at 1.0 mol% Pd catalyst loading.¹⁸ By contrast when Cole-Hamilton and co-workers used the related orthopalladated benzylphosphine complex **8c**, they found no activity with the activated substrate 4-chloroacetophenone and a good TON of 2 700 with 4-chlorobenzaldehyde, but at the expense of selectivity; the product is contaminated with substantial amounts of 1-(4-chlorophenyl)-

1-phenylmethanol and 1,4-biphenyl-1-phenylmethanol.¹⁹ They also found that the complexes **8b** and **c** are good catalysts in the Heck coupling of aryl bromides with TONs of up to 3.6 million in the coupling of 4-bromoacetophenone with *n*-butylacrylate and 16 900 with the more electronically challenging substrate, 4-bromoanisole.

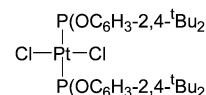
By contrast with palladium, platinum catalysts show almost no activity in coupling reactions. One reason for this is that the higher oxidation states of platinum are more stable than those for palladium, disfavoured reductive elimination processes.²⁰ If this is indeed the reason for the poor activity then π -acidic phosphite or phosphinite ligands may well be expected to increase the rate of such processes and render the use of platinum catalysts viable. This indeed proved to be the case and again orthometallation appears to be important with the complexes **9** showing enhanced activity compared with the non-cyclometallated complex **10** in the Suzuki coupling of aryl bromides.²¹ The best activity was observed with complex **9b** which gives a TON of 2.5 million, under air, in the coupling of phenylboronic acid with 4-bromoacetophenone. Substantially lower activity is seen with electronically deactivated aryl bromides, but some activity is even seen with activated aryl chlorides.



9a: $R = \text{OC}_6\text{H}_3\text{-2,4-}{}^t\text{Bu}_2$

b: $R = \text{Ph}$

c: $R = {}^i\text{Pr}$

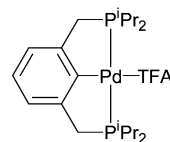


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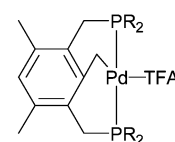
Palladium *P,C,P*-pincer complexes

Shortly after the early development of κ^2 -*P,C* palladacyclic catalysts, κ^3 -*P,C,P*-pincer complexes were shown to be active by Milstein and co-workers. They demonstrated that the complexes **11** and **12** could be used to good effect at low catalyst loadings in the Heck coupling of aryl iodides and activated aryl bromides.²² Thus TONs of up to 528 700 are seen in the coupling of iodobenzene with methyl acrylate catalysed by **10a**; changing to 4-bromobenzaldehyde leads to a drop in TON to 113 300. The *P,C,P*-pincer complex **13**, based on the metallation of a saturated ring, also shows good activity in the Heck coupling of aryl iodides and activated and non-activated aryl bromides.²³ Indeed in all cases its performance was better than that obtained with related unsaturated system **11**.

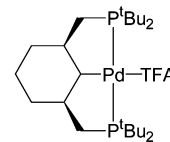
A chiral bis(phosphine) pincer complex, **14**, has been synthesised, but it proved to be a poor catalyst for the



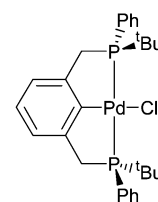
11



12a: $R = {}^i\text{Pr}$
b: $R = {}^t\text{Bu}$



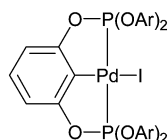
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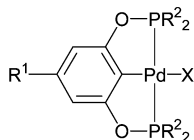
14

asymmetric Heck reaction, giving an ee of only 3% in the coupling of phenyl triflate with 2,3-dihydrofuran.²⁴

Since more π -acidic ligand systems seem to be beneficial to the performance of κ^2 -*P,C* palladacyclic catalysts, it may be logical to assume that more π -acidic *P,C,P*-pincer ligands should also show enhanced activity. This indeed appears to be the case; Shibasaki and co-workers showed that the bis-(phosphite)-*P,C,P*-pincer-based complex **15** gives TONs of up to 8.9 million in the Heck coupling of *n*-butyl acrylate with iodobenzene, and 980 000 with the more electron rich iodide 4-iodoanisole.²⁵



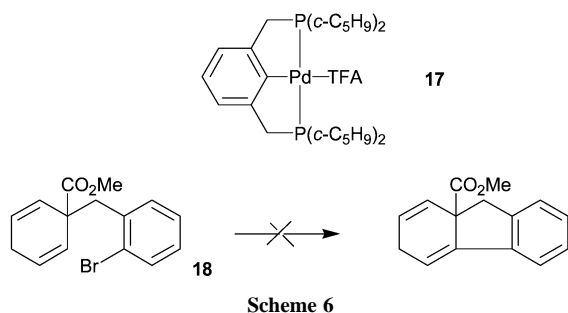
15: Ar = C₆H₄-4-OMe



16a: R¹ = H; R² = Ph; X = TFA
b: R¹ = Me; R² = Ph; X = TFA
c: R¹ = H; R² = ⁱPr; X = Cl

As seen with the *P,C*-palladacycles, while phosphite-based systems show better activity than very electron-rich phosphine analogues, 'fine-tuning' of the electronic properties can have a further beneficial effect on the performance. Thus the bis-(phosphinite) pincer complexes **16a** and **b** not only show good activity in the Suzuki coupling of deactivated and activated aryl bromides but also activated aryl chlorides.²⁶ Meanwhile the analogous complex **16c** can be used for the Heck coupling of *deactivated* aryl chlorides such as 4-chloroanisole.²⁷ Interestingly, the TONs seen with complexes **16a** and **b** are 1–3 orders of magnitude lower than those obtained with the notionally related *P,C*-palladacycles **5c** and **d**.¹⁷ Additionally while **16c** evidently has no problem coupling deactivated chloride substrates such as 4-chloroanisole, complex **5d** is very poor in this regard. This may indicate that very different catalytic manifolds are followed by the two distinct catalyst families.

A caveat was put on the use of palladium *P,C,P*-pincer complexes as catalysts in the Heck reaction when Bergbreiter, Sulikowski and co-workers demonstrated that not only is the complex **17** no use as a catalyst in the *intra*-molecular Heck coupling of the diene **18** (Scheme 6), but also that the catalyst is

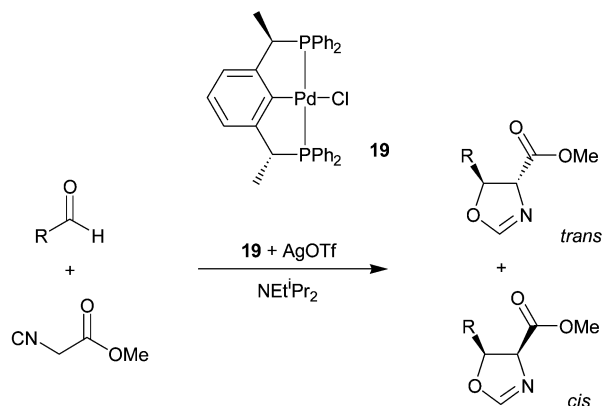


Scheme 6

inhibited by the presence of the substrate.²⁸ Further experiments demonstrated that it is the diene portion of the substrate that leads to the inhibition, presumably by binding strongly to the palladium centre. By contrast, a simple Pd(OAc)₂/PPh₃ system is unaffected and is able to catalyse the *intra*-molecular Heck coupling of **18** effectively.

When the catalyst simply acts as a Lewis acid and does not undergo a change in oxidation state during the catalytic cycle then stereoselectivity can occur with chiral *P,C,P*-pincer complexes. Thus complex **19** shows reasonable enantioselectivity in the aldol reaction of methylisocyanoacetate with aldehydes. In nearly all cases the *trans*-oxazoline products predom-

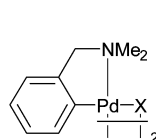
inate with ees up to 31%. The maximum ee observed for the *cis* product is 77% (Scheme 7).²⁹



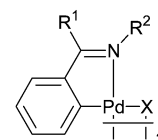
Scheme 7

L,C-palladacyclic, *L,L,C*- and *L,C,L*-pincer based catalysts (L = N, S)

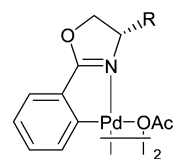
Catalytic activity is by no means limited to phosphorus-containing palladacycles. For instance we, and later others, found that the orthopalladated *N,N*-dimethylbenzylamine complex **20a** could be used as a catalyst for the Heck coupling of aryl bromides.^{14,30,31,32} Later Milstein demonstrated that the imine containing catalysts **21** and **22** could be used in the Heck reaction with aryl iodide and bromide substrates.³³ While TONs of up to 1.4 million are seen in the coupling of iodobenzene with methyl acrylate, the activity dropped by about one order of magnitude on changing to bromobenzene.



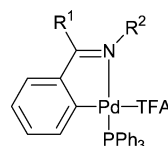
20a: X = Cl
b: X = TFA



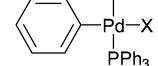
21a: R¹ = Me; R² = ⁱPr; X = TFA
b: R¹ = H; R² = ⁱPr; X = TFA



22a: R = H
b: R = CH₂ⁱPr
c: R = ⁱPr



23a: R¹ = Me; R² = ⁱPr; X = TFA
b: R¹ = H; R² = ⁱPr; X = TFA

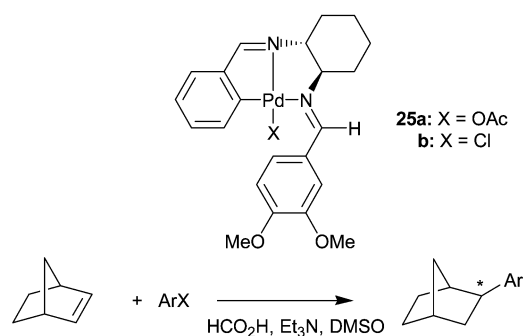


24a: X = Cl
b: X = TFA

The catalyst **21a** also shows good activity in the Suzuki coupling of aryl bromides with TONs of up to 840 000 and 136 000 for the coupling of phenylboronic acid with 4-bromoacetophenone and 4-bromoanisole respectively.³⁴ We have found that the triphenylphosphine adducts **23** of the dimeric complexes **21**, show substantially increased activity in the Suzuki reaction compared with the parent dimers.^{35,36} Thus while complex **21a** gives a TON of 320 000 in the coupling of 4-bromoanisole with phenylboronic acid, the phosphine adduct

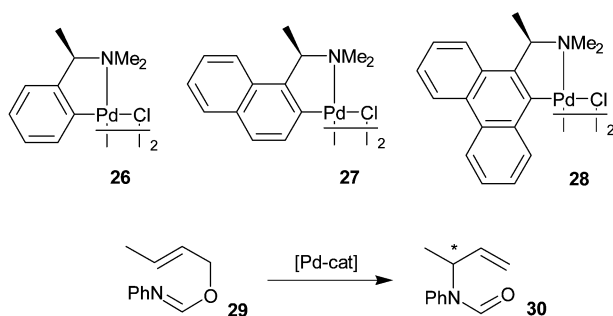
23a gives a value of 480 000 for the same reaction. Changing the ketimine ligand for an aldimine analogue is beneficial to catalyst performance with the complex **23b** giving a TON of 820 000. The complex **20b** also shows reasonably good activity, however this is again enhanced when triphenylphosphine is incorporated to give the complex **24b**.³⁶ A similar increase in activity is seen when complex **24a** is used in the Heck coupling of aryl iodides in place of the parent dimer **20a**.³²

Recently Navarro and co-workers synthesised the chiral *N,N,C*-complexes **25**, based on (1*R*,2*R*)-1,2-diaminocyclohexane and applied them to Heck-type coupling reactions.³⁷ These catalysts show reasonable activity in the coupling of methyl acrylate with aryl iodides and activated aryl bromides but poor activity with the non-activated substrate bromobenzene. Attempts to apply these catalysts to the asymmetric hydroarylation of 2-norbornene (Scheme 8) showed no enantioselectivity, with



Scheme 8 Catalytic hydroarylation of 2-norbornene.

all optical rotations measured close to zero. By contrast when the chiral amine-based palladacycles **26–28** are used as catalysts in the asymmetric Claisen rearrangement of the allyl imidate **29** then the chiral amide **30** is obtained with an ee of up to 79% (Scheme 9).³⁸ The reason why good enantioselectivity is seen



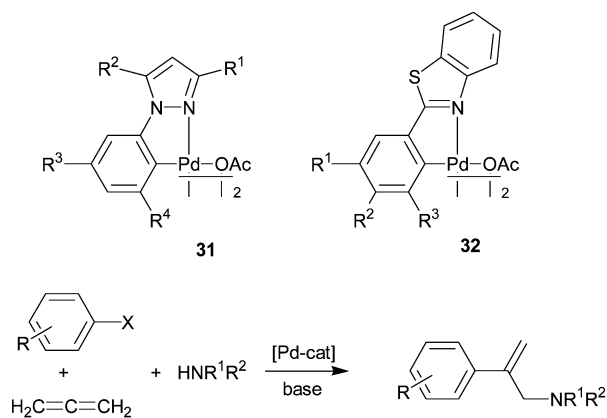
Scheme 9

here is almost certainly due to the fact that the catalysts act as Lewis acids and do not undergo any redox processes.

In addition to showing activity in the Heck coupling of iodobenzene, palladacycles of the types **31** and **32**, based on pyrazole and benzothiazole, show activity in the three-component cascade process outlined in Scheme 10.³⁹

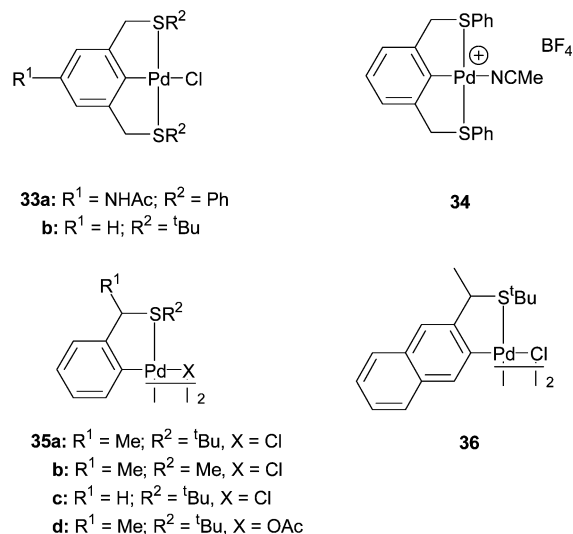
Once again Bergbreiter demonstrated that the attempted use of an *N,C*-palladacycle, namely complex **22c**, in the *intra*-molecular Heck coupling of the diene **18** (Scheme 6) is unsuccessful, again presumably due to inhibition by the substrate.²⁸

S,C-based palladacyclic complexes have also been successfully applied as catalysts in C–C bond forming reactions. Bergbreiter demonstrated that the *S,C,S*-pincer complexes **33a** and **34** could be used as catalysts for the Heck coupling of aryl iodides with TONs up to 70 000, although no activity was observed with aryl bromides.⁴⁰ By contrast Dupont and Monteiro showed that the more electron-rich system **33b** could be used to good effect in the coupling of the deactivated



Scheme 10

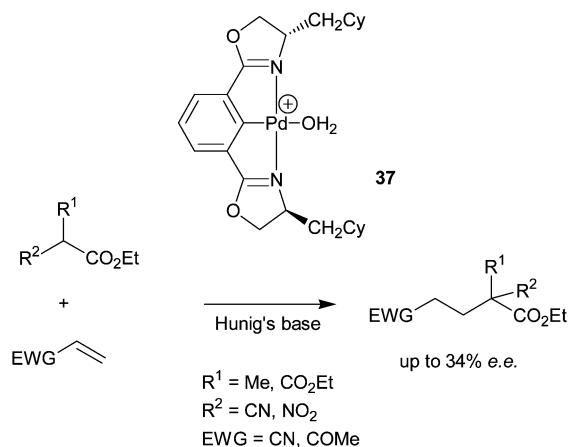
substrate 4-bromoanisole in Suzuki coupling reactions.⁴¹ Similarly, good activity is seen with the complexes **35** and **36**. Catalyst **35a** even shows some, albeit very limited, activity with the deactivated aryl chloride substrate, 4-chloroanisole. This catalyst also shows good activity in the sterically challenging coupling of bromomesitylene with 2-tolylboronic acid.



Again attempts to use chiral analogues in the asymmetric Heck reaction failed with essentially no ees observed in the coupling of 3,4-dihydro-2*H*-pyrane with aryl bromides or iodides catalysed by resolved (*R*)-**35a**.⁴² Enantioselectivity is once again observed if the metal centre is not required to undergo redox processes during the catalytic cycle. Thus the complex **37** shows moderate enantioselectivity in asymmetric Michael coupling reactions (Scheme 11).⁴³

Aryl chlorides as substrates

While a few of the complexes outlined above show some activity in the coupling of aryl chlorides, the best of them only give moderate performances with electronically challenging (electron-rich) substrates. This is unfortunate as such substrates tend to be far more readily available and considerably cheaper than their bromide or iodide counterparts. The problem with aryl chlorides is that the C–Cl bonds are significantly stronger than those of aryl bromides, which are in turn stronger than those of aryl iodides.⁴⁴ Consequently oxidative-addition reactions of aryl chlorides are much less facile than those of the heavier congeners. There has recently been a large body of work focussed on the development of catalysts that can activate aryl chlorides,⁴⁵ but in most cases reasonably high catalyst loadings are required. This means that the advantage of using a cheap substrate may be lost because of the high cost of the palladium



Scheme 11

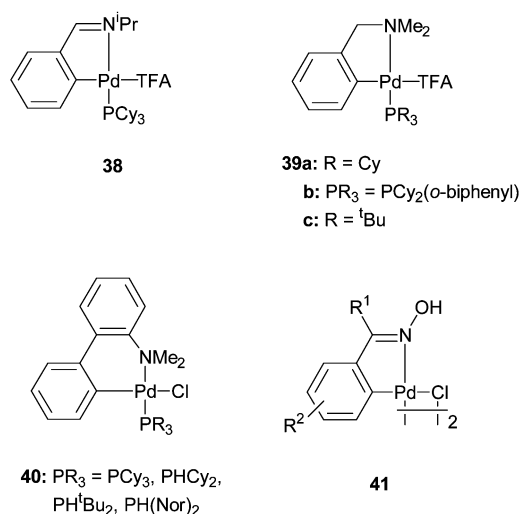
and the ligands. In addition, for fine chemical synthesis, Pd loadings must be kept to a minimum to reduce product cleanup costs. Given that a large proportion of the interest in palladacyclic catalysts is due to the fact that, in general, they can be used in low loadings, it is not surprising that this class of complexes has recently had a substantial role to play in aryl chloride activation.

As discussed earlier examples of the complexes **1**, **5**, **8**, **16** and **35** show reasonable activity with some, usually less electronically challenging substrates, while the pincer complex **16c** shows good activity in the Heck coupling of 4-chloroanisole at 0.67 mol% Pd.²⁴ Having found that the triphenylphosphine adducts of orthometallated amines and imines, complexes **23** and **24**, are good catalysts for the Suzuki coupling of deactivated aryl bromides,^{35,36} we wondered whether di- and trialkylphosphine derivatives would show any activity in the coupling of aryl chloride substrates. The complexes **38**, **39a** and **b** are readily prepared by reaction of the parent dimers with the appropriate phosphines.^{46,47} While complex **39c** forms under these conditions, isolation of the pure complex is not possible due to the extreme lability of the phosphine. All of the catalysts are active in the Suzuki coupling of aryl chlorides with complex **39a** showing TONs of up to 8000 in the coupling of phenylboronic acid with 4-chloroanisole,⁴⁶ making it, at the time, one of the most active aryl chloride coupling catalysts.⁴⁸ The performances of **39b** and **c** in this reaction were lower, despite both phosphine ligands being excellent in their own right for the Suzuki coupling of aryl chlorides.⁴⁹ By contrast catalysts formed *in situ* from palladium acetate and tricyclohexylphosphine show very little activity.^{50,47} The catalysts **39** were also screened for activity in Buchwald–Hartwig amination reactions of 4-chloroanisole and catalyst **39c**, formed *in situ*, shows the best activity in this regard and nearly seven times the activity of a catalyst formed *in situ* from palladium acetate and P^tBu₃.⁴⁷

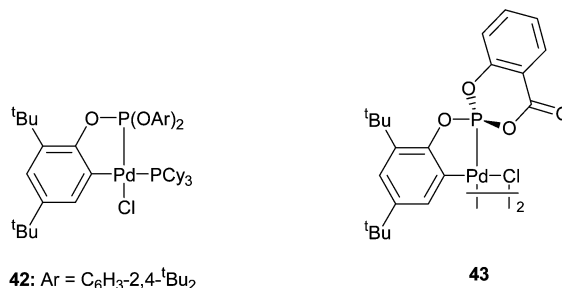
Subsequently Indolese and Studer reported the application of related catalysts, such as **40**, in a range of coupling reactions with deactivated aryl chloride substrates and found that secondary as well as tertiary phosphine adducts show good activity.⁵¹

In the absence of any added phosphine ligands, the parent amine complex **20b** shows essentially no activity in the coupling of 4-chloroanisole with phenylboronic acid.⁴⁶ By contrast Nájera demonstrated that the oxime-containing complexes **41** shows activity in this reaction, giving a TON of 40, provided that tetrabutylammonium bromide and water are present in the reaction mixture.⁵² The significance of this result will be discussed later.

Despite the fact that complexes of the type **5** show, at best, very limited activity in the coupling of activated and non-activated aryl chlorides,¹⁸ we recently found that catalyst **42**, typically formed *in situ* from complex **5a** and one equivalent per palladium of PCy₃, shows extremely high activity in the Suzuki



coupling of deactivated aryl chloride substrates, with TONs of up to about 49 000 observed in the coupling of phenylboronic acid with 4-chloroanisole.^{53,54} Similarly catalysts formed *in situ* from **5a** and either P^tBu₃ or PCy₂(*o*-biphenyl) show good activity, but not as high as that observed with tricyclohexylphosphine. When the precursor **5a** is replaced with the more electron-deficient complex, **43**, then even greater catalyst performance results.⁵⁴ Thus the catalyst formed *in situ* from **43** and tricyclohexylphosphine shows TONs of up to 128 000 and 2 million in the coupling of phenylboronic acid with 4-chloroanisole and 4-chloroacetophenone respectively.



The high activity obtained with these catalysts is not due to any spectacular increase in rate, but rather to greater catalyst longevity. What is the basis of this increased longevity? Given that the rate determining step is oxidative addition and assuming that the active catalyst is a Pd(0) species (see later) then the catalyst spends most of its time 'resting' in a zerovalent state. This 'resting' state will be stabilised both thermodynamically and kinetically by the reversible coordination of the π -acidic triarylphosphite ligand. Decoordination of the phosphite would give a low coordinate, electron rich complex readily able to oxidatively add the aryl chloride substrate and thus re-enter the catalytic manifold. This argument is supported by the data in Fig. 2 which shows plots of conversion vs. time in the coupling of 4-chloroanisole with phenylboronic acid, catalysed by palladacycles with varying π -acidity of the orthometallated ligand. As can be seen, the catalyst longevity is dependent on the π -acidity which falls in the order **43** > **5a** > **5c** > **5d**. In addition when the complex **39a** is used, which has no π -acidic co-ligand, then there is no activity observed after two hours, however addition of ligand **6** to complex **39a** *in situ* leads to a substantial increase in longevity.⁵³

While the catalyst **42** also shows good activity in Stille coupling of aryl chloride substrates, the activity is no better than that observed with catalysts formed *in situ* from tricyclohexylphosphine and palladium acetate.⁵⁵ This is not surprising since the rate-determining step here does not appear to be oxidative addition, but rather trans-metallation. Therefore the catalyst resting state will be Pd(II) which may not be expected to

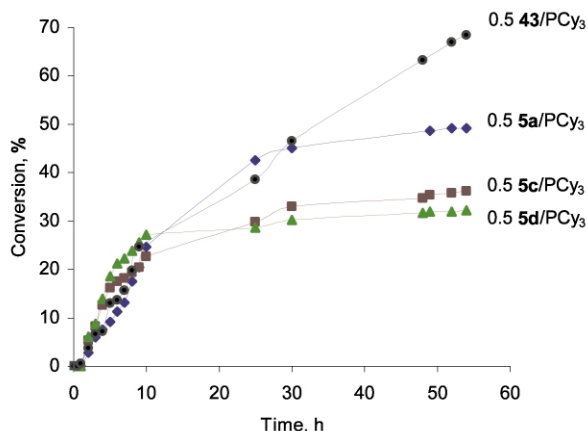


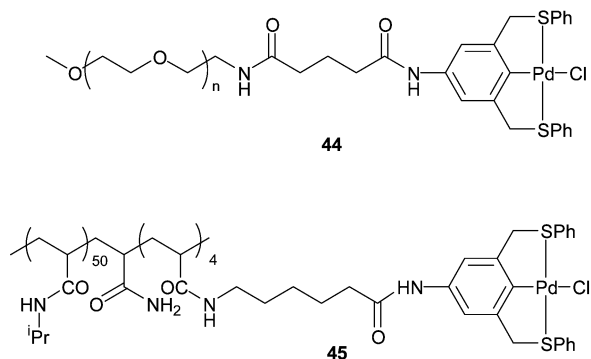
Fig. 2 Suzuki coupling of 4-chloroanisole with phenylboronic acid at 0.001 mol% Pd loading.

be significantly stabilised by the presence of π -acidic co-ligands.

Recyclable catalysts?

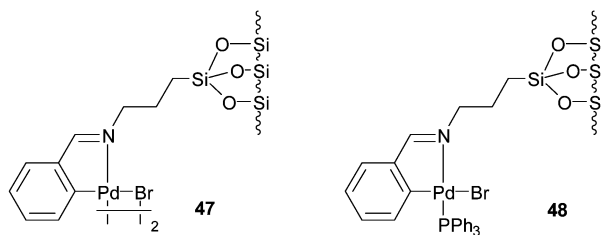
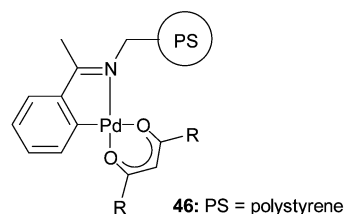
The high thermal stability of palladacycles combined with their high activity in coupling reactions makes them obvious candidates for recycling protocols. In general, the results from this research have been somewhat equivocal; while some systems do appear to be recyclable, they only work for the coupling reactions of the 'easy' substrates, aryl iodides. When more challenging reactions are investigated then invariably no real recyclability is observed.⁵⁶

Bergbreiter and co-workers synthesised the polymer-modified catalysts **44** and **45** which seem to show recyclability in coupling reactions of aryl iodides. Thus complex **44** at 1 mol% Pd loading shows recyclability over three runs in the Heck coupling of iodobenzene with methylacrylate or styrene,⁴⁰ while complex **45** shows recyclability at 0.2 mol% Pd in both Heck and Suzuki coupling of aryl iodides over 4 to 5 runs.⁵⁷ Interestingly, in these cases, the highest activity was not seen until after the first run which may indicate a protracted induction period. In addition there is not a great disparity between the total TONs recorded and the maximum TON recorded for homogeneous analogues. For true recyclability, the catalyst should show a far greater total TON compared with the maximum TON for a homogeneous analogue. Therefore it is not possible at this stage to determine whether these catalysts are truly recyclable or whether they act as slow-release sources of Pd(0).



Another route to recyclable catalysts is to immobilise them on solid supports. Nowotny and co-workers opted for this method and produced the polystyrene-immobilised catalyst **46**.⁵⁸ The catalyst shows comparable activity to homogeneous analogues in the Heck coupling of iodobenzene with styrene. In both homogeneous and heterogeneous cases an induction time was observed, demonstrating that the complexes are not the true

active catalysts but rather pre-catalysts that are activated *in situ*. In the case of **46** no recyclability is observed; the catalyst recovered by filtration showed no activity in a second run. By contrast the *filtrate* showed activity comparable to that obtained in the first run, but without the presence of an induction time. The authors concluded that the likely active catalyst is nanoparticulate palladium stabilised by an ammonium salt; such species have been shown previously to be active catalysts in the Heck reaction.⁵⁹



We have found similar effects in the Suzuki coupling of aryl bromides.³⁵ The silica-immobilised catalysts **47** and **48** were synthesised and their application to the Suzuki coupling reaction studied. Figure 3 indicates that while the complex **48**

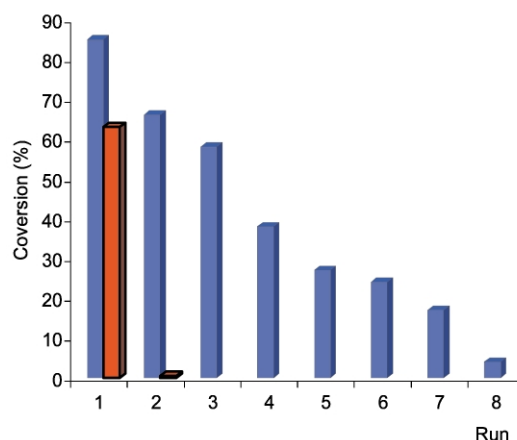


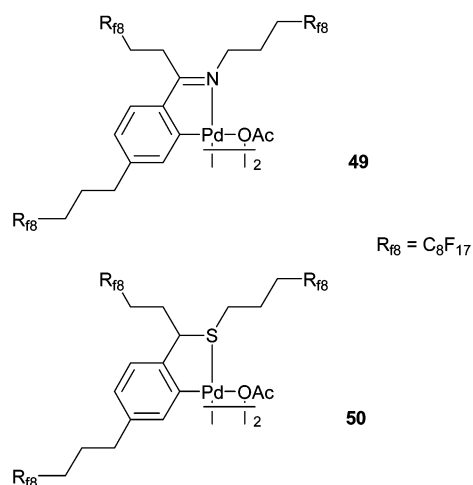
Fig. 3 Use and recyclability of the catalysts **47** (■ 0.31 mol% Pd) and **48** (■ 0.0013 mol% Pd) in the Suzuki coupling of 4-bromoanisole with phenylboronic acid.

shows some limited reuse, the phosphine adduct shows no recyclability, but much higher initial activity. In addition we too find that the filtrate from reactions catalysed by **48** is catalytically active. This demonstrates that at least some part of the catalysis is performed away from the support, which may merely be functioning as a slow-release source of active catalyst.

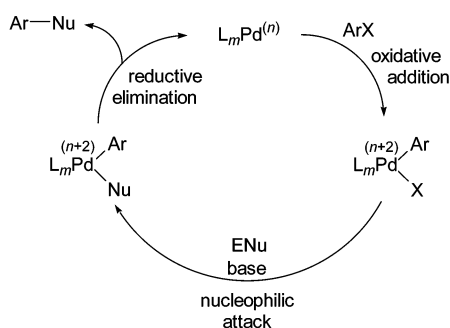
Similar results were found by Gladysz and co-workers when they attempted to recycle the perfluoroalkyl-modified imine- and thioether-based palladacycles **49** and **50** in Heck and Suzuki coupling reactions; activity fell off from one run to the next.⁶⁰

Mechanistic considerations

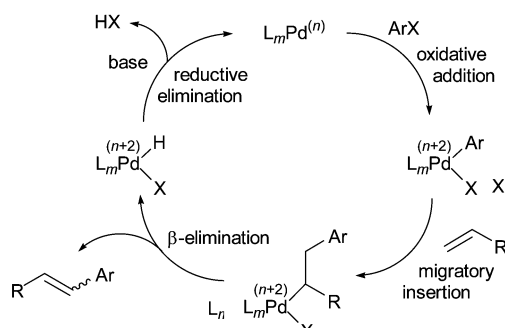
In light of the observations obtained in the recycling studies outlined above, it seems apparent that in most, if not all cases palladacycles are not the 'true' active catalysts, but rather are



pre-catalysts that undergo an activation process. This is further supported by the observation that chiral analogues show no stereoselectivity in asymmetric coupling reactions that proceed *via* redox processes, which implies that the ligands may not even be in the coordination sphere of the active catalysts. This brings us to the question that has been raised on many an occasion during the study of palladacyclic pre-catalysts — do the coupling reactions proceed *via* ‘classical’ Pd(0)/Pd(II) pathways or *via* Pd(II)/Pd(IV) cycles? In order to address this question it is best to separate the coupling reactions into Heck-type reactions where a nucleophile is coupled with an aryl halide and the Heck reaction proper, which differs mechanistically. Highly simplified catalyst cycles for these two processes which show only the ordering of the major reaction steps are shown in Schemes 12 and 13 respectively.



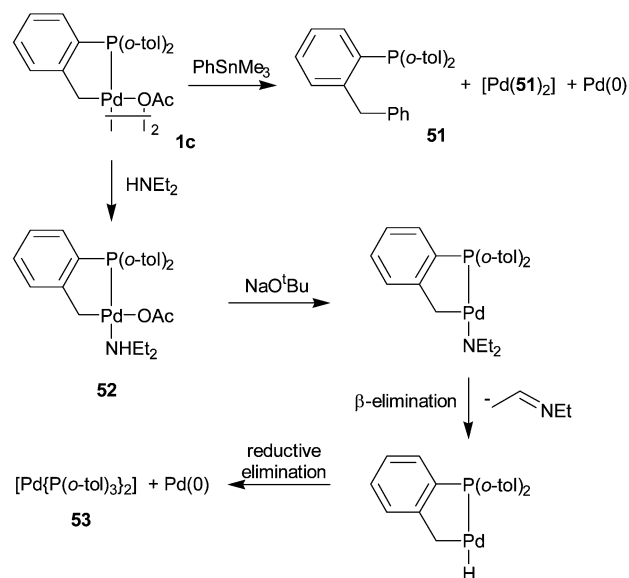
Scheme 12 Highly simplified catalytic cycle for Suzuki (ENU = Ar'B(OH)₂), Stille (ENU = Ar'SnR₃), Kumada (ENE = Ar'MgX), Negishi (ENU = Ar'ZnX), Sonogashira (ENU = HCCR) and Buchwald–Hartwig amination (ENU = HNRR') reactions.



Scheme 13 Highly simplified catalytic cycle for the Heck reaction.

In the case of the reactions other than the Heck reaction then the answer now appears to be relatively straightforward; the weight of evidence strongly supports Pd(0)/Pd(II) pathways of the type shown in Scheme 12 with $n = 0$. How then are the palladacycles reduced to palladium(0) species? Louie and

Hartwig demonstrated that complex **1c** reacts with phenyltributyltin to generate the new ligand **51** both free and coordinated to a palladium(0) centre (Scheme 11).¹⁰ They also showed that **1c** reacts with HNEt₂ to give the amine adduct **52** which is deprotonated in the presence of NaO^tBu to give the palladium(0) complex **53** *via* β -elimination of the amide ligand (Scheme 14). The activities of **1c**, **52** and **53** are identical in the



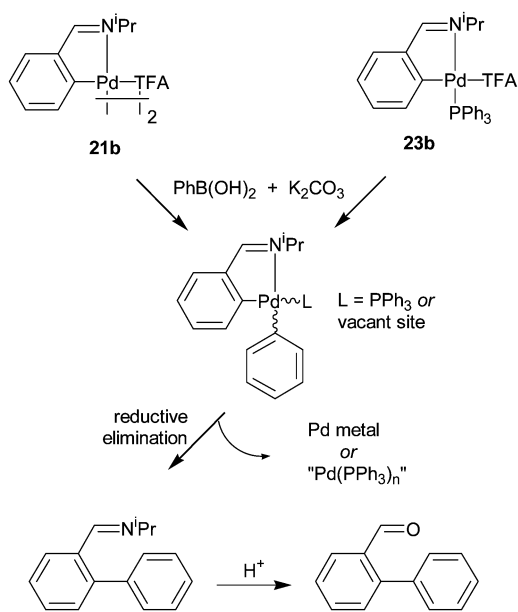
Scheme 14

amination of 4'-bromobenzophenone with *N*-methylaniline, indicating a common Pd(0) catalyst. When β -elimination is not possible, *i.e.* when diphenylamine is used as the coupling partner, complex **1c** is inert whereas the pre-formed Pd(0) catalyst **53** is active.

Having found that the silica-supported complexes **47** and **48** are not recyclable, but rather appear to act as slow-release sources of active catalysts in solution, we investigated the reactions of the model compounds **21b** and **23b** with components of the Suzuki reaction.³⁵ No reaction was observed with activated aryl bromides, indicating that the Pd(II) complexes show no propensity to enter a Pd(II)/Pd(IV) manifold. However, reaction of the complexes with phenylboronic acid in the presence of base, followed by hydrolytic work-up, leads to the formation of 2-phenylbenzaldehyde, presumably by the mechanism shown in Scheme 15, indicating that the palladacycles are readily reduced under the conditions employed in the Suzuki reaction. Such pathways are not without precedent — some years earlier Rao demonstrated a similar reaction with aryl lithium reagents acting as the nucleophiles could be used to generate 2-arylbenzaldehydes.⁶¹ It is likely that, in the presence of PPh₃, the active catalysts are low coordinate phosphine adducts, while in the absence of the co-ligands the catalyst is probably palladium metal in colloidal form. This is supported by the observation that aliquots taken from a Heck reaction catalysed by the fluoros ponytail-modified imine palladacycle **49** and analysed by TEM show the presence of palladium nanoparticles.^{60b}

Similar studies with complex **5b** again show that it does not oxidatively add aryl bromides, but is readily reduced to palladium(0) by phenylboronic acid/base mixtures. In this case GC/MS analysis showed the presence of the new phosphinite ligand PPh₂(OC₆H₄-2-Ph), formed by reductive-elimination of the orthometallated aryl group.¹⁷

While these stoichiometric studies may be persuasive, they may not accurately represent the true situation under catalytic conditions. Evidence that such pathways are indeed active in the Suzuki reaction was provided by analysis of a coupling of 4-chloroanisole with phenylboronic acid catalysed by complex **39a**. This reaction not only shows nearly quantitative formation



Scheme 15

of the Suzuki product but also the presence of the 2-arylated ligand, $\text{Me}_2\text{NCH}_2(\text{C}_6\text{H}_4\text{-2-Ph})$ (~63% based on **39a**), presumably formed by a mechanism related to that shown in Scheme 15.

Given that both imine- and amine-based palladacycles react with aryl boronic acids in the presence of base to generate Pd(0) species, it seems highly likely that the oxime-based palladacycles, **41**, reported by Nájera,⁵² undergo a similar activation process. However, these catalysts are able to couple deactivated aryl chloride substrates such as 4-chloroanisole. Interestingly they are only able to do this in the presence of tetrabutylammonium bromide. This salt is known to stabilise palladium nanoparticles that are able to couple aryl halide substrates.⁵⁹ It is possible that what these data are showing us is that palladium nanoparticles are capable of acting as aryl chloride coupling catalysts. However, under the conditions employed, palladium acetate — a good source of palladium nanoparticles — is not active.⁵² This may conceivably be due to different modes or rates of formation of palladium colloids from different palladium starting materials. In support of this we found that palladium acetate, in the absence of any co-ligands but in the presence of tetrabutylammonium bromide and water, can indeed be employed to similar effect in the Suzuki coupling of aryl chlorides under different reaction conditions.⁶²

In the case of the Heck reaction the issue of whether palladacyclic catalysts follow a Pd(0)/Pd(II) or a Pd(II)/Pd(IV) pathway (Scheme 13, $n = 0$ or 2 respectively) was not, at first, as clear cut. 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 that maybe Pd(0) is not being formed.^{1b} Following the coupling of 4-bromobenzaldehyde with *n*-butyl acrylate catalysed by **1c** by ³¹P NMR spectroscopy, Herrmann found no evidence for the formation of zero-valent palladium–phosphine complexes. The only complexes observed were **1a** and mononuclear ‘ate’ complexes formed by the reaction of dimers with anions present in the reaction.⁵ All this data implied that it might be possible that the catalysis occurs via a Pd(II)/Pd(IV) pathway. Such a pathway was described by Shaw,¹² and invokes the reversible attack of a nucleophile (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) centre. However, as yet, there is essentially no evidence that such a pathway is operative. Oxidative addition of aryl halides to the

complexes **1** is not observed,^{1b} suggesting a simple mechanism such as that shown in Scheme 13 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 catalysts. Indeed the order of activity of the palladacycles **1** with varying anions is **1c** ($\text{X} = \text{OAc}$) > **1a** ($\text{X} = \text{Br}$) > **1d** ($\text{X} = \text{Cl}$),^{1b} which is the opposite trend for the thermal stability of Pd(II) salts with these anions.⁶³ The alkyl substituted palladacycles **54** are more electron-rich than the complex **1c**, therefore if a Pd(II)/Pd(IV) pathway is operative they should show higher activity. In practice they are poorer catalysts.⁶⁴ In addition alkyl-substituted complexes such as **54** are more thermally stable than the complex **1c** which further supports the suggestion that the true catalysts are formed by a thermal reduction process.

In summary, while it is still not entirely possible to dismiss any contribution from Pd(II)/Pd(IV) pathways, the evidence accumulated so far indicates that it is highly unlikely that such mechanisms can account for the high catalyst activity observed with palladacycles. Far more likely is that palladacycles act as stable, inexpensive, clean sources of low-coordinate palladium(0).

Outlook for the future

It seems highly likely that given the success of palladacyclic catalysts in coupling reactions, that further advances will be made in this area. Their general air and moisture stability allows them to be easily handled and stored, yet their ability to undergo rapid activation processes leading to the clean generation of highly reactive species makes them ideal candidates for use in industrial processes. To date such applications have remained limited, but the situation may well change as more in depth investigations into areas such as catalyst longevity, substrate tolerance and the ability to couple deactivated aryl chlorides at very low catalyst loadings are performed.

Acknowledgments

I would like to thank Drs Ann Bingham and Simon Coles at the EPSRC crystallography service, Southampton for their substantial help in the preparation of the front cover picture.

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