Halide and pseudohalide effects in Pd-catalysed cross-coupling reactions

Ian J. S. Fairlamb,*[a] Richard J. K. Taylor,[a] Jose Luis Serrano[b] and Gregorio Sanchez[c]

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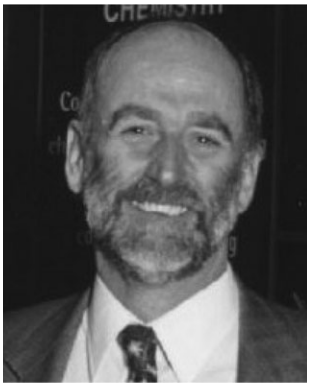
The presence of halide and pseudohalide anions dramatically affects the outcome of transition-metal catalysed reactions, both in terms of selectivity and activity. In this perspective, the roles and effects of these anionic ligands in topical and important Pd-catalysed cross-coupling reactions involving the formation of C–C bonds, *e.g.* Sonogashira, Stille and Suzuki–Miyaura cross-coupling, will be described. The use of imidate anions (derived from succinimide, maleimide and phthalimide) in several different classes of neutral and anionic Pd catalysts/precatalysts will be highlighted.

1 Introduction

Great progress has been made in the development of Pd-catalysed processes that facilitate the formation of C–C bonds.[1] Reactions such as Sonogashira, Stille and Suzuki–Miyaura cross-coupling are commonly employed in synthetic routes to complex natural products, advanced materials and therapeutic agents.[2] In drug development, Pd-catalysed processes represent a significant proportion of reactions carried out in industry, in lead discovery particularly, with aromatic and heteroaromatic transformations accounting for the majority of these reactions.

Through use of electron-rich and sterically bulky two-electron donor ligands such as t-Bu_3P[3] and N-heterocyclic carbenes,[4] which primarily increase the nucleophilicity of the Pd^0 active species in the oxidative addition step, the substrate scope of these reactions is now arguably greater than traditional C–C bond-forming processes. The steric and electronic properties of these neutral donor ligands also influence the

Ian Fairlamb (born 1975, UK) was appointed to a lectureship in Organic Chemistry at York in late 2001, following a successful PhD under the guidance of Dr J. Dickinson investigating the rational design and synthesis of squalene synthase inhibitors (1999), and productive post-doctoral research stay with Prof. G. C. Lloyd-Jones, studying the mechanisms of various Pd-catalysed processes (2000–01). At the age of 28, he was awarded the prestigious Meldola Medal and Prize by the Royal Society of Chemistry (2004) to recognize outstanding independent contributions in the application of transition-metal catalysed reactions, particularly involving palladium, to the synthesis of medicinally relevant molecules and natural products. He is a recipient of a Royal Society University Research Fellowship (started October 2004) for "understanding, controlling and exploiting unusual observations in Pd-catalysed reactions". Dr Fairlamb is associate editor for Tetrahedron (UK region) and a senior scientific reporter for Specialist Periodical Reports: Organometallics.



Richard Taylor graduated from the University of Sheffield and then carried out his PhD under the supervision of Dr D. Neville Jones working in the area of thiasteroid synthesis. After postdoctoral periods with Dr Ian T. Harrison (Syntex Research) and Professor Franz Sondheimer, University College London, he was appointed to a lectureship at the Open University in Milton Keynes. A move to the University of East Anglia, Norwich followed and in 1993 he was appointed to a Chair of Organic Chemistry at the University of York. Professor Taylor's research interests centre on the synthesis of bioactive natural products and the development of new synthetic methodology. His awards include the Royal Society of Chemistry's Hickinbottom Fellowship (1985–87), Heterocyclic Award (1999), the Tilden Medal (1999/2000) and the Pedler Lectureship (2007/2007). Professor Taylor is the immediate President of the RSC Organic Division and the current UK Regional Editor of Tetrahedron.

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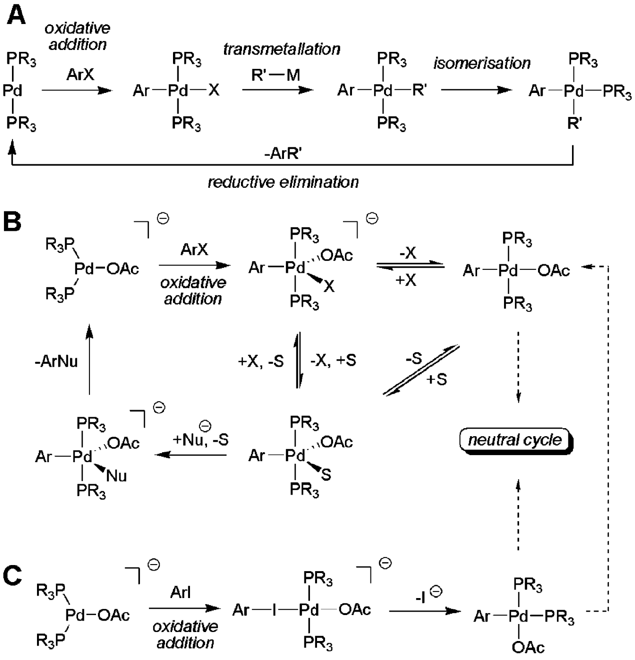
[a] *Department of Chemistry, University of York, Heslington UKYork. E-mail: ijsf1@york.ac.uk; Fax: +44 1904 432516; Tel: +44 1904 434091*
[b] *Departamento de Ingeniería Minera, Geológica y Cartográfica, Área de Química Inorgánica, Universidad Politécnica de Cartagena, 30203 Cartagena, Spain*
[c] *Departamento de Química Inorgánica, Universidad de Murcia, 30071 Murcia, Spain*

José L. Serrano was born in Valencia, Spain in 1970. He graduated from the University of Murcia in 1993 and then studied for a PhD degree (1997) at the same University under the supervision of Prof. G. López and G. Sánchez. As a postdoctoral fellow he stayed for a short time with Prof. Jon R. Dilworth at the Inorganic Chemistry Laboratory (Oxford) working with hybrid P,S-ligands. He became a lecturer in Cartagena in 1999 and since then he has independently focused on the synthesis of novel palladium(II) imidate complexes, and explored the hemilabile properties of several classes of P,N- and P,O-ligands.

Gregorio Sánchez was born in La Unión (Murcia), Spain in 1951. He graduated from the University of Murcia in 1975 and he obtained his PhD degree (1984) under the supervision of Prof. G. López and G. García in the same University. Since becoming a lecturer in 1987 he has held different positions, rising to the rank of Professor of Inorganic Chemistry at the University of Murcia. His research interests include the preparation and reactivity of hydroxo-complexes of group 10 metals (Ni, Pd and Pt) complexes with hybrid and/or hemilabile ligands. He has interests in the synthesis and catalytic properties of imidate–palladium complexes.



Scheme 1 (A) Neutral Pd^0/Pd^{II} catalytic cycle (textbook mechanism); (B) anionic Pd^0/Pd^{II} catalytic cycle *via* five-coordinate intermediates; (C) anionic Pd^0/Pd^{II} catalytic cycle *via* four-coordinate intermediates.

intrinsic stability/reactivity of all Pd intermediates found in the appropriate catalytic cycle.[5]

Halide counterions, as anionic ligands, play a significant role in Pd-catalysed cross-coupling processes, as well as in other transition-metal-mediated reactions.[6] Tuning of the halide or halide mimetic (pseudohalide) is, however, often neglected. This is to some extent surprising given that specific halides should have the propensity to affect the intrinsic reactivity of Pd intermediate species, whether they be Pd^0, Pd^I, Pd^{II}, Pd^{III} or Pd^{IV}. Halides are involved directly in the intimate steps of the catalytic cycle(s) where differential effects are expected. Put simply, the role of the halide in oxidative addition and transmetallation would undoubtedly be different. A fundamental question is what obvious function does the halide ligand play? The answer is complex and dependent on a number of factors. The various properties exerted by halide ligands need to be considered, *e.g.* (i) steric effects; (ii) electronic properties (either σ- and π-bonding); (iii) polarizability; (iv) nucleophilicity; (v) the *trans*-effect.[6] Which property or combination of properties dominates subtly depends on individual reaction systems. Comprehensive evidence for the involvement of halide/pseudohalide anions in Pd-catalysed cross-coupling comes from the decisive mechanistic studies conducted by Amatore and Jutand.[7] In the presence of halides, *e.g.* chloride or bromide, the existence of an alternative catalytic cycle involving tricoordinated anionic complexes such as $L_2Pd^0Cl^-$ and $L_2Pd^0OAc^-$, has been shown to be operative, in addition to the classic textbook mechanism involving a neutral Pd^0/Pd^{II} catalytic cycle, mechanism A, Scheme 1 (the anionic Pd^0/Pd^{II} catalytic cycle is depicted in mechanism B, Scheme 1).

The halide/pseudohalide may be liberated from the organohalide, as is the case in most cross-coupling reactions, particularly where a metal salt is produced as the side-product. Alternatively, the halide could be derived from Pd^{II} precatalysts, *e.g.* $Pd(Ph_3P)_2Cl_2$ or $Pd(OAc)_2$. The reduction of $Pd(Ph_3P)_2Cl_2$ in THF[8] affords $Pd^0(PPh_3)_2Cl^-$, in addition to $Pd^0(PPh_3)_2Cl_2^{2-}$ and the dimer complex $Pd^0_2(PPh_3)_4(\mu\text{-}Cl)_2^{2-}$. Reactivity differences for halides have been established for $Pd(Ph_3P)_2X_2$ complexes (where X = I, Br or Cl) and the order of stabilisation of the halide on the anionic Pd^0 species is I > Br > Cl.[9] DFT calculations provide some support for the anionic Pd^0/Pd^{II} catalytic cycle,[10] though it has been predicted that the most energetically favorable mechanism for the oxidative addition of aryl halides to Pd-catalysts is *via* a stable four-coordinate anionic intermediate and not five-coordinate Pd-intermediate (Mechanism C, Scheme 1). This has not been observed experimentally, however.

In consideration of anionic Pd^0 species, differences in the reactivity of acetate and trifluoroacetate anions has also been established for the precatalysts $Pd(OAc)_2$ and

$Pd(OCOCF_3)_2$.[11] Firstly, the rate of formation of $Pd^0(PAr_3)_2(OCOCF_3)^-$ from $Pd(OCOCF_3)_2$ is higher than the rate of formation of $Pd^0(PAr_3)_2(OAc)^-$ from $Pd(OAc)_2$. In oxidative addition reactions of PhI, $Pd^0(PAr_3)_2(OCOCF_3)^-$ is intrinsically more reactive than $Pd^0(PAr_3)_2(OAc)^-$. The oxidative addition intermediate *trans*-$PhPd^{II}(OCOZ)(PPh_3)_2$ ($Z = CH_3$ or CF_3) is in equilibrium with the cationic complex *trans*-$[PhPd^{II}(PPh_3)_2(DMF)]^+$, the equilibrium constant of which is directly affected by the stability of the carboxylate anion.

Acetate and triflate anions exhibit prominent effects in the degradation (reduction) of palladacycles, which are commonly used as precatalysts; both catalyst activity and lifetime have been shown to be dependent on the nature of the specific pseudohalide.[12] In the absence of the pseudohalide, the reduced species undergoes rapid reaction to form an inactive metallic Pd precipitate. Anion binding essentially stabilizes the mononuclear L_nPd^0 species or soluble palladium clusters/colloids, which act as a reservoir[13] for catalytically active Pd^0 species (neutral or anionic), particularly at high reaction temperatures.[14,15]

Another role for halides/pseudohalides in cross-coupling reactions could be to facilitate an alternative catalytic cycle, *e.g.* a Pd^{II}/Pd^{IV} cycle. Here the specific type of ligands would have a dramatic effect in what many consider as a controversial catalytic cycle for these processes.[16] It should be stated that numerous Pd^{IV} complexes are known,[17] though the majority of these possess hard nitrogen ligands, usually bidentate systems such as TMEDA, which essentially stabilise the higher oxidation state of Pd^{IV}, which is likely to be a *mandatory* requirement. We will not elaborate any further on the participation of these catalytic cycles in cross-coupling processes.

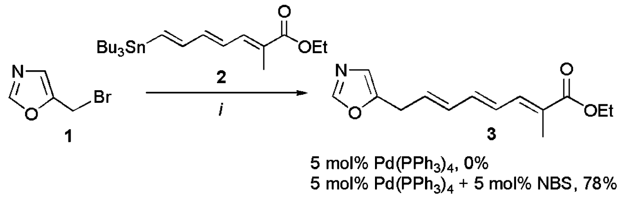
Having set the scene for the crucial role played by halides/pseudohalides in Pd-catalysed cross-coupling processes, the following sections will focus on our interests in exploiting anionic ligand effects. It is the purpose of this perspective to emphasize our initial findings and very recent results from Stille, Sonogashira and Suzuki cross-coupling processes, which draw attention to the powerful effects exerted by imidate type anions (derived from succinimide, maleimide and phthalimide).

2 Stille coupling

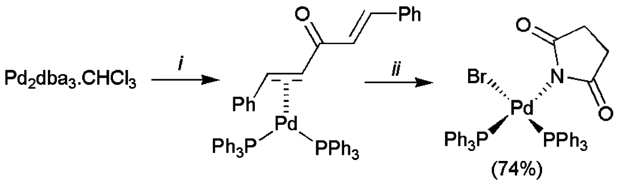
2.1 Initial findings

Our interest in halide/pseudohalide effects was sparked by the serendipitous discovery that catalytic quantities of *N*-bromosuccinimide (NBS) were required for successful Stille cross-coupling of oxazole bromide **1** with trienyl organostannane **2** to give **3** (Scheme 2).[18] Without this additive the reaction failed, which is quite an unusual observation.

It was eventually found that trace quantities of NBS oxidatively added to $Pd(PPh_3)_4$ to give *cis*-$Pd(PPh_3)_2$(*N*-Succ)Br, a complex originally reported by Serrano *et al.*,[19] which efficiently promotes this quite tricky transformation. It should be noted that the reaction does not proceed with catalytic NBS without an added Pd^0 source. The complex may be efficiently prepared by reaction of $Pd_2dba_3 \cdot CHCl_3$ with PPh_3 (1 : 4), followed by oxidative addition with NBS to give *cis*-$Pd(PPh_3)_2$(*N*-Succ)Br (Scheme 3).[20] The yield of this product can be improved to 82% through use of the more activated Pd^0 source, $Pd(dm\text{-}dba)_2$, developed separately by Fairlamb *et al.* (dm-dba = *E*,*E*-3,3′,5,5′-tetramethoxydibenzylidene acetone).[21]



Scheme 2 Original finding involving NBS accelerative effect. *Reagents and conditions*: (i) **1** (1 equiv.), **2** (1.05 equiv.), $Pd(PPh_3)_4$ (0.05 equiv.), NBS (0.05 equiv.), toluene, reflux, 20 h.



Scheme 3 Synthesis of *cis*-$Pd(PPh_3)_2$(Br)N-Succ. *Reagents and conditions*: (i) $Pd_2(dba)_3 \cdot CHCl_3$ (0.5 equiv.), PPh_3 (2 equiv.), CH_2Cl_2, 25 °C, 0.2 h; (ii) NBS (1 equiv.), 0.2 h.

A critical question is raised by this finding: is *cis*-$Pd(PPh_3)_2$(*N*-Succ)Br a precatalyst to a neutral or anionic Pd^0 catalyst? or a catalyst in other catalytic cycles? Although we are not able to fully address this yet, a number of fascinating observations point to a crucial role played by both the bromide and succinimide ligands in *cis*-$Pd(PPh_3)_2$(*N*-Succ)Br.

Before elaborating further, it is worth stressing the potential bonding modes exhibited by succinimidate, and related derivatives, to transition-metal centres. Generally four coordination modes are feasible (**I–IV**, Fig. 1).

Imidate ligands also impart unique properties to various metal centres,[22] as they are capable as acting as monodentate or bidentate ligands; in the latter mode they are hemilabile, displaying similar coordination behaviour to acetate. Such modes of coordination are expected to stabilise catalytic

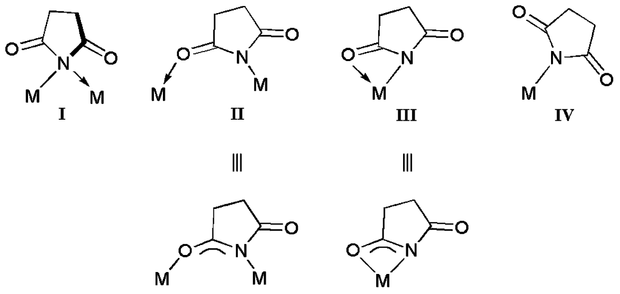
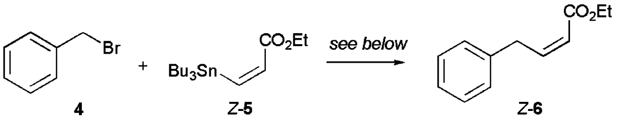


Fig. 1 Potential coordination modes of succinimidate and related ligands to metal centres.

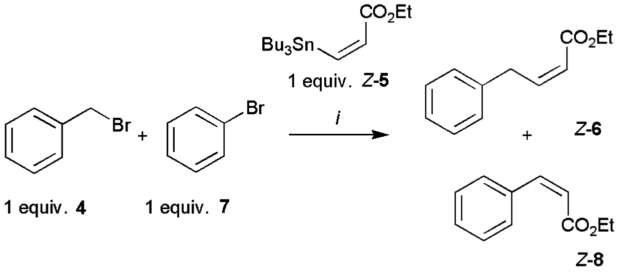
Table 1 Comparison of catalytic activity of various Pd^0 and Pd^{II} sources[a]



Entry	Complex	Time/h	Yield[b] (%)
1	$Pd(PPh_3)_4$[c]	18	17
2	$Pd(OAc)_2$, PPh_3[d]	18	16
3	$Pd_2(dba)_3 \cdot dba$, PPh_3[e]	18	13
4	$Pd(PPh_3)_2Br_2$	18	23
5	$Pd(PPh_3)_2(Bn)Br$	18	49[i]
6	$Pd(PPh_3)_2(Bn)Cl$	18	66
7	$Pd(PPh_3)_4$, NBS[f]	18	83
8	$Pd(PPh_3)_4$, NCS[f]	18	61
9	$Pd(PPh_3)_4$, NIS[f]	18	33
10	$Pd_2(dba)_3 \cdot dba$, PPh_3, NBS[f]	18	76
11	$Pd(PPh_3)_2$(*N*-succ)Br	1.5	99
12	$Pd(PPh_3)_2$(*N*-succ)I	18	56
13	$Pd(PPh_3)_2$(*N*-phthal)Br[g]	1.5 (18)	72 (98)
14	$Pd(PPh_3)_2$(*N*-succ)$_2$	48	10
15	$Pd(PPh_3)_2$(*N*-phthal)$_2$	48	11
16	NBS with no added palladium[h]	3	2

[a] *Reaction conditions*: Benzyl bromide **4** (1 equiv.), organostannane *Z*-**5** (1.2 equiv.), [Pd] (0.05 equiv.), toluene, 60 °C. [b] Isolated yield after KF work-up and chromatography. Note: a DBU/I_2/Et_2O work-up for this specific reaction results in rapid regio- and stereo-isomerisation (<2 min). [c] Freshly prepared from $Pd(PPh_3)_2Cl_2$, NH_2NH_2 in EtOH at 120 °C. [d] 3 equiv. of PPh_3 were used wrt to Pd. [e] 2 equiv. of PPh_3 were used wrt to Pd. [f] 1 equivalent of the *N*-halosuccinimide was added wrt to Pd. [g] Numbers in brackets are the time after 18 h reaction and the corresponding yield, respectively. [h] NBS (5 mol %) was added under the reaction conditions described in *a*—but in the absence of palladium (new glassware was employed for this reaction). [i] The *Z*-**6** : *E*-**6** ratio was *ca.* 1 : 1.6.

Table 2 Competition experiment between aryl and benzylic bromides[a]



Entry	Complex	Yield (%)	
		Z-**6**	*Z*-**8**(*E*-**8**)
1	$Pd(PPh_3)_2$(*N*-succ)Br	86	0
2	$Pd(PPh_3)_4$	0	39 (9)
3	$Pd(PPh_3)_2Br_2$	0	21 (15)
4	$Pd(PPh_3)_2(Bn)Br$	16	36
5	$Pd(PPh_3)_2$(*N*-succ)Br + LiBr	45	22

[a] *Reaction conditions*: (i) [Pd] (0.05 equiv.), toluene, reflux, 18 h.

intermediates. Modes **I** and **III** are less well known, whereas modes **II** and **IV** are more common, and representative of all the catalyst structures described in this perspective.

To compare the catalytic activity of *cis*-$Pd(PPh_3)_2$(*N*-Succ)Br against other standard catalysts/precatalysts a benchmark reaction of benzyl bromide **4** with *Z*-organostannane **5** at 60 °C to give *Z*-**6** was selected (Table 1). Use of the following catalyst systems $Pd(PPh_3)_4$, $Pd(OAc)_2/PPh_3$, $Pd_2dba_3 \cdot dba/PPh_3$ and $Pd(PPh_3)_2Br_2$ gave generally poor yields (entries 1–4). The fact that $Pd(PPh_3)_2(Bn)Br$ gave a modest yield with poor selectivity is intriguing, as this precatalyst represents the formal oxidative addition intermediate from the reaction of $Pd^0(PPh_3)_2$ with **4** in the neutral Pd^0/Pd^{II} cycle (although $Pd(PPh_3)_2(Bn)Cl$ gave *Z*-**6** in reasonable yield, entry 6). The striking effect of added *N*-halosuccinimides to $Pd(PPh_3)_4$ can be seen in entries 7–10. The addition of NBS to $Pd(PPh_3)_4$ gave *Z*-**6** in 83% yield (entry 7). Other *N*-halosuccinimides, NCS and NIS, also promote the reaction, but to a lesser extent (61 and 33%, respectively, entries 8 and 9). The prepared complex *cis*-$Pd(PPh_3)_2$(*N*-Succ)Br exhibits the best catalytic activity by some margin (entry 11). *trans*-$Pd(PPh_3)_2$(*N*-Succ)I gave a lower yield (56%), underlining the importance associated with the halide (entry 12). A difference between phthalimidate and succinimidate is also apparent (entries 11 and 13). It was then determined that $Pd(PPh_3)_2$(*N*-succ)$_2$[23] and $Pd(PPh_3)_2$(*N*-phthal)$_2$[24] were poor catalysts/precatalysts (entries 14 and 15), emphasising a requirement for halide.

Reactivity differences were recorded for various substrates using *cis*-$Pd(PPh_3)_2$(*N*-Succ)Br when compared against other Pd catalysts/precatalysts. The specific type of organostannane tends to affect the extent of any differences in catalytic activity (and associated yield).[18b]

In further studies it was established that *cis*-$Pd(PPh_3)_2$(*N*-Succ)Br was a poor catalyst for the cross-coupling of aryl halides with various organostannes. Indeed, in a competition experiment in which one equiv. of **4** and one equiv. of bromobenzene **7** were reacted with *Z*-**5** it was found that *cis*-$Pd(PPh_3)_2$(*N*-Succ)Br preferentially reacts with **4** (Table 2).

By contrast, the complexes $Pd(PPh_3)_4$, $Pd(PPh_3)_2Br_2$ and $Pd(PPh_3)_2(Bn)Br$ show preferential selectivity towards **7** (entries 1–3). The addition of LiBr to the reaction mediated by $Pd(PPh_3)_2$(*N*-succ)Br results in a selectivity switch (entry 5). This selectivity switch can only be accounted for by an alternative mechanism to the other evaluated catalysts/precatalysts.

A thorough review detailing the mechanism(s) of the Stille reaction has recently been described by Espinet and Echavarren;[5] several discussions concerning the role of 14- and 16-electron intermediates has also been reported.[25] Although we cannot at this stage propose a clear mechanism for *cis*-$Pd(PPh_3)_2$(*N*-Succ)Br, the experimental observations made so far rule out a Pd^{III} catalytic cycle involving radical intermediates; the order of reactivity with respect to *para*-substituted benzyl bromides with *Z*-**5** is OMe > H > NO_2, which mirrors the reactivity sequence previously established by Milstein and Stille (both OMe and NO_2 should be able to stabilise a benzylic radical).[26]

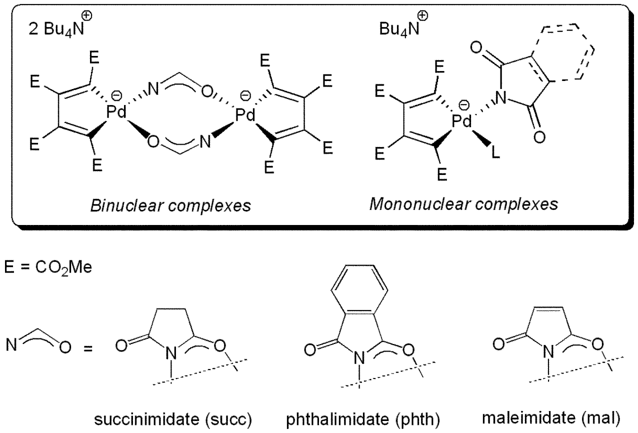


Fig. 2 Binuclear and mononuclear anionic palladacyclopentadienyl complexes containing bridging (*N*,*O*-) and terminal (*N*-) imidate ligands, respectively.

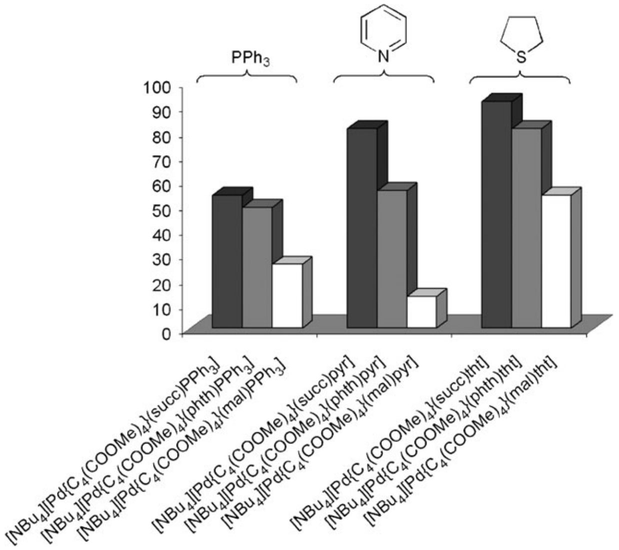


Fig. 3 Effect of donor ligand in mononuclear complexes. Conversion recorded after 1 h by HRGC. Key: (■) succinimidate; (▨) phthalimidate; (☐) maleimidate.

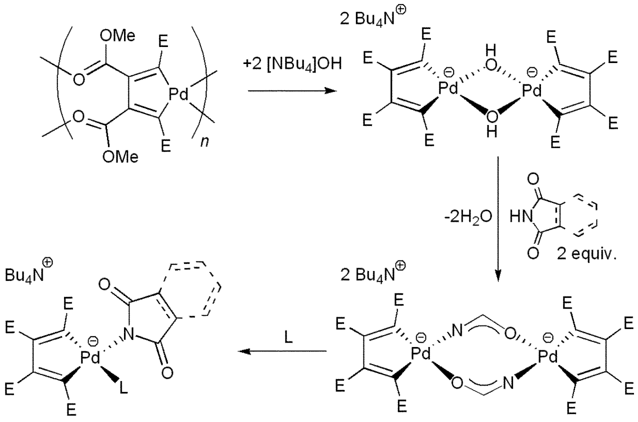
2.2 Second-generation catalysts

Having established the catalytic activity of *cis*-$Pd(PPh_3)_2$(*N*-Succ)Br it became clear that other Pd^{II} complexes possessing imidate ligands could promote Stille coupling. Anionic palladacyclic structures containing succinimidate, maleimidate and phthalimidate anionic ligands were selected for an assessment of their catalytic activity (Fig. 2).[27]

These complexes are readily prepared by reaction of the well known[28] polymeric complex $[Pd\{C_4(COOMe)_4\}]_n$ with *n*-Bu_4NOH to give $[NBu_4]_2[Pd_2\{C_4(COOMe)_4\}_2(\mu\text{-}OH)_2]$, followed by imide deprotonation to generate the binuclear complexes (Scheme 4).[29] All of these anionic Pd^{II} complexes are air-, light- and moisture-stable and can be stored for many months at room temperature.

Stille cross-coupling of **4** with *Z*-**5** to give *Z*-**6** was once more used as a benchmark reaction (using 5 mol% Pd). The catalytic activity of the mononuclear complexes was expected to be higher than the binuclear complexes, given that they contain an activating donor ligand. However, it was established that electron-releasing ligands slowed down the rate of catalysis (Fig. 3).[30] Moreover, pronounced pseudohalide effects were observed. The order of reactivity in this particular series is succinimidate > phthalimidate > maleimidate.

We debated whether the donor ligand was required at all, leading us to test the binuclear complexes. These complexes surprisingly exhibit higher catalytic activity (note that $[Pd\{C_4(COOMe)_4\}]_n$ is a poor catalyst for this reaction, which perhaps relates to solubility) (Fig. 4). Again there is a significant pseudohalide effect, which is more evident on analysis of reactions after only 0.75 h. It was also possible to compare the imidate ligand effects with the hydroxy, chloro and bromo binuclear complexes ($[NBu_4]_2[Pd_2\{C_4(COOMe)_4\}_2(\mu\text{-}X)_2]$,[28a] where X = OH, Cl or Br). The lowest conversions were recorded for the hydroxo complex, which could be associated with the faster degradation rate of this complex, or explained by a more pronounced difference of this ligand *vs.* the other halides/pseudohalides. Indeed, this comparative study of the behaviour of the halides/pseudohalides highlighted the most



Scheme 4 Synthesis of binuclear and mononuclear anionic palladacyclopentadienyl complexes.

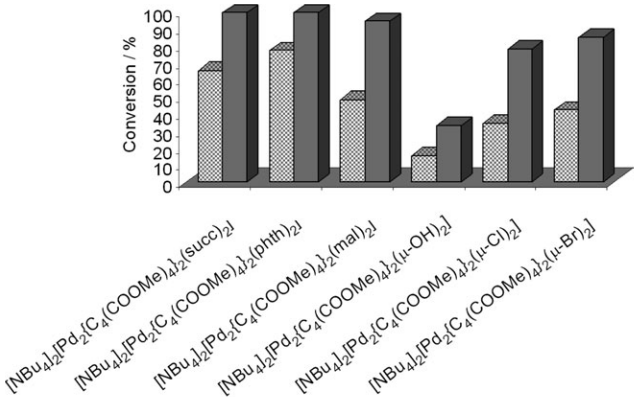
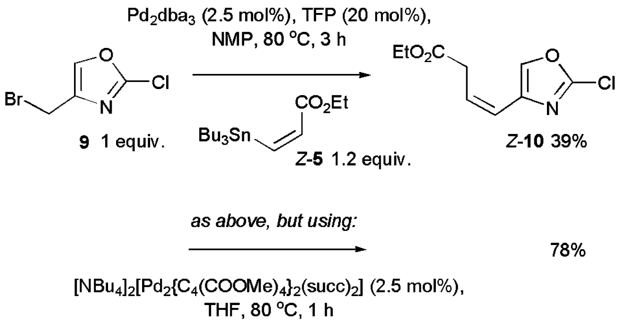


Fig. 4 Effect of halides/pseudohalides in binuclear complexes (light grey checkered columns represent percentage conversion after 0.75 h; dark grey filled columns represent percentage conversion after 3 h).



Scheme 5 Effect of halides/pseudohalides in binuclear complexes.

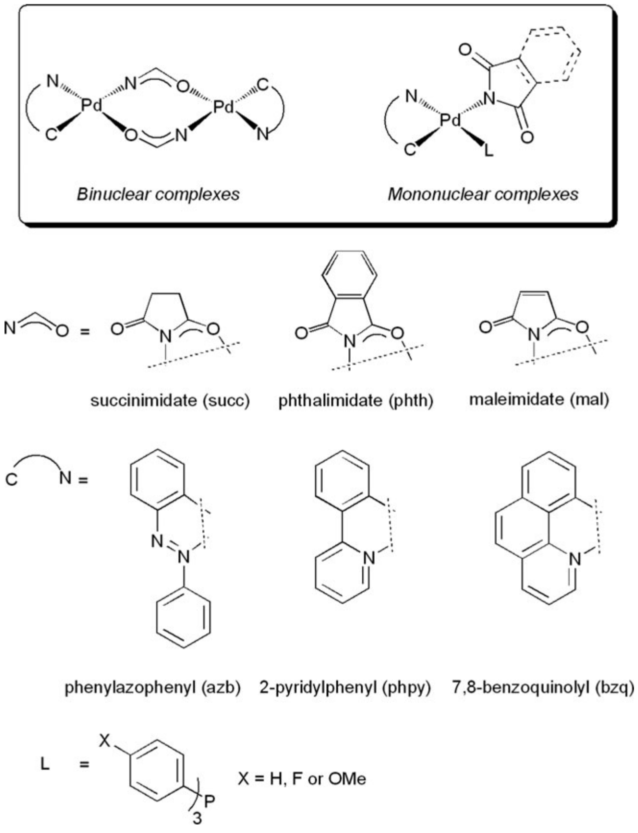


Fig. 5 Mono- and binuclear cyclometallated palladium(II) complexes with bridging (N,O) and terminal (N) imidate ligands.

striking effects observed in all of the studies conducted thus far, implying an important role for the anionic ligands in the catalysis. Somewhat surprisingly, the addition of co-catalytic quantities of Cu^I (10 mol%) dramatically reduces the rate of catalysis, as does the addition of CsF (catalytic or stoichiometric amounts), which would have been expected to activate the organostannane. It remains unclear at this stage why this occurs and further studies are in progress to probe this observation. In DMF, this situation changes however, and high catalytic activity is only observed in the presence of catalytic Cu^I and stoichiometric CsF, similar to the activity recorded for $Pd(PPh_3)_4$ by Baldwin and co-workers.[31] Curiously, in this solvent, these additives are required for effective cross-coupling—negligible reaction is seen when $[NBu_4]_2[Pd_2\{C_4(COOMe)_4\}_2(succ)_2]$ is used alone in DMF at 60 °C. Here, there is clearly a dramatic solvent effect.

A range of substrates may be effectively coupled using $[NBu_4]_2[Pd_2\{C_4(COOMe)_4\}_2(succ)_2]$ as a catalyst. Indeed, a significant enhancement in yield was recorded in the Stille cross-coupling of a challenging halogenated oxazole **9** with *Z*-**5** to give *Z*-**10** (Scheme 5); note that double bond migration into conjugation with the oxazole occurs (in a surprisingly *Z*-stereoselective manner).[32]

It was always assumed that the palladacyclopentadienyl structure would degrade under the reaction conditions. However, the detection of side-products derived from it has not been acheived. Based on the comprehensive studies by Elsevier and co-workers,[33] the detection and isolation of the palladacyclopentadienyl unit should be expected in some form, assuming that it is degraded under the reaction conditions. It is consequently of interest to note that all binuclear palladacyclopentadienyl complexes are poor catalysts for Suzuki–Miyaura cross-coupling of activated and deactivated aryl halides, where decomposition and rapid formation of Pd black is observed (note: the initial rates are high, to 40–50% conversion), decomposition is observable after *ca.* 30 min).[34] This is not the case for Stille cross-coupling reactions carried out in toluene at 60 °C.

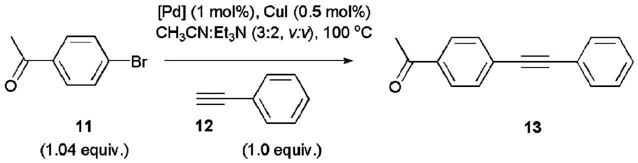
In DMF in the presence of catalytic Cu^I and stoichiometric CsF, one anticipates that the organostannane transmetallates to give the more reactive organocuprate species.[31] However, the pronounced halide/pseudohalide effects detailed above undoubtedly indicates a role for the anionic ligands in the catalytic cycle. The absence of any degradation products from the palladacyclopentadienyl unit could lead one to suggest an alternative mechanism over the classical Pd^0/Pd^{II} catalytic cycle. However, it is evident that further mechanistic studies are required to clarify this observation.

3 Sonogashira and Suzuki–Miyaura coupling

3.1 Application of palladacycles containing imidate anions

A library of binuclear cyclometallated palladium complexes of general formula $[\{Pd(\mu\text{-}NCO)(C^\wedge N)\}_2]$, containing asymmetric imidato–NCO bridging units, and mononuclear complexes of general formula $[Pd(C^\wedge N)(imidate)(L)]$, were easily prepared (Fig. 5).[35] This facilitated an assessment and correlation of three structural components in the palladacyclic structure: (i) the importance of the $C^\wedge N$ backbone; (ii) the pseudohalide effect; (iii) the donor ligand effect (phosphine, L).

The catalytic activity of twenty palladacycles were assessed in the Sonogashira cross-coupling[36] of 4-bromoacetophenone



Scheme 6 Sonogashira cross-coupling reaction used as a benchmark for palladacyclic imidate complexes (shown in Fig. 5).

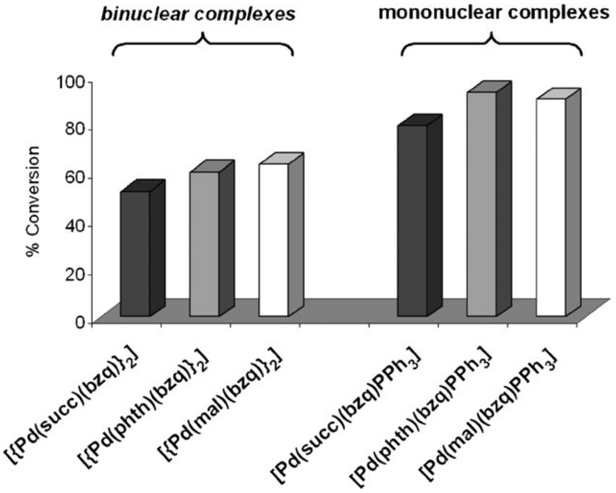


Fig. 6 Pseudohalide effects in binuclear and mononuclear Pd^{II} complexes). Key: (■) succinmidate; (▨) phthalimidate; (□) maleimidate.

11 with phenylacetylene **12** to give **13**. The conversion into **13** was compared after 2 h by HRGC (Scheme 6).

These reactions proceed more rapidly with a Cu^{I} co-catalyst, although product **13** is usually free of phenylacetylene dimer under Cu^{I}—free conditions (similar yields are seen after 5 h). To illustrate the importance of the different structural components in the palladacyclic complexes, the catalytic activity against this benchmark reaction was correlated with points i–iii (*vide supra*).

A pseudohalide effect can be seen by comparing the binuclear complexes (Fig. 6). The order of reactivity is maleimidate > phthalimidate > succinimidate, for complexes containing a 7,8-benzoquinolyl backbone. For the mononuclear complexes containing a 7,8-benzoquinolyl backbone and PPh$_3$ donor ligand, a trend again emerges, while it is apparent that succinimidate is the least active, maleimidate and phthalimidate exhibit similar catalytic activity. These results point to the importance associated with the presence of the PPh$_3$ ligand, however.

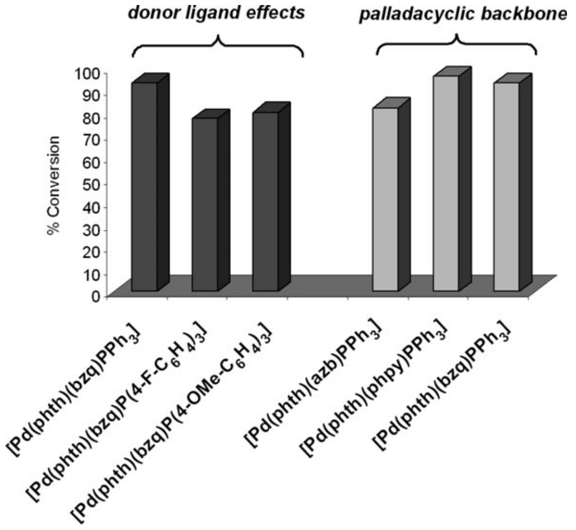
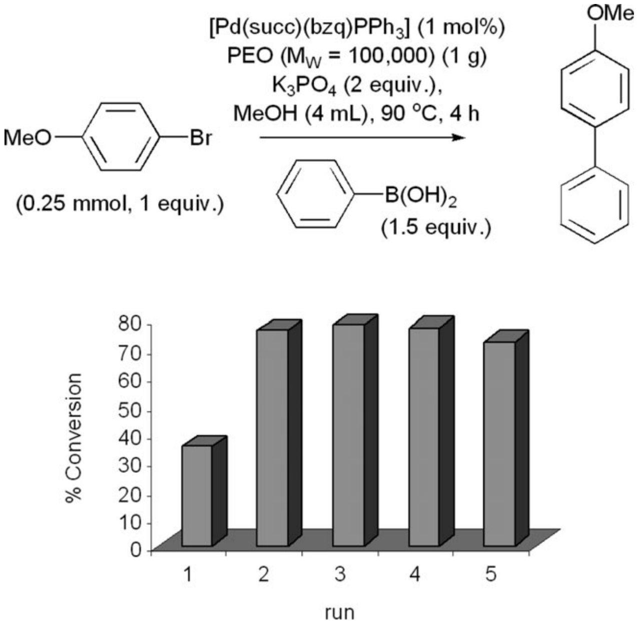


Fig. 7 Donor ligand and *C^N* backbone ligand effects in mononuclear Pd^{II} complexes.



Scheme 7 Catalyst recycling in Suzuki–Miyaura cross-coupling.

In mononuclear complexes containing a phthalimidate ligand and 7,8-benzoquinolyl backbone, alteration of the donor ligand affected the catalytic activity (Fig. 7). Perhaps surprisingly, PPh$_3$ was the best ligand when compared with electron withdrawing and electron releasing PAr$_3$ ligands. Subtle differences are apparent when the *C^N* backbone was altered for mononuclear complexes containing phthalimidate and PPh$_3$ ligands.

Overall, these results show that comparable catalytic activity is observed irrespective of the structure of the palladacycle, indicating that under the reaction conditions, similar catalytically active Pd species are formed. In terms of catalyst design this is a finding that is difficult to accept. However, species corresponding to the degradation of the palladacyclic backbone have been detected by MS. It is consequently thought that catalyst activity mirrors the degradation rate resulting in the release of low concentrations of catalytically active Pd^{0}.[14] These results are in keeping with recent studies on the degradation of palladacyclic structures.[37]

Lesser differences in catalyst activity are observed for binuclear and mononuclear complexes in Suzuki–Miyaura cross-coupling of activated and deactivated aryl bromides with phenylboronic acid.[35a]

Of practical interest is the fact that catalyst recycling of the Pd species, produced as a result of palladacycle degradation, is possible using a poly(ethylene oxide) (PEO)/methanol method developed by Monteiro and co-workers for Pd(OAc)$_2$/PPh$_3$.[38] The initial reaction of 4-bromoanisole with phenylboronic acid to give 4-methoxybiphenyl (run 1) shows modest conversion (Scheme 7). At the end of the reaction, the product can be extracted into a non-polar phase, with the Pd-catalyst remaining in the polar phase. Recharging the polar phase with new

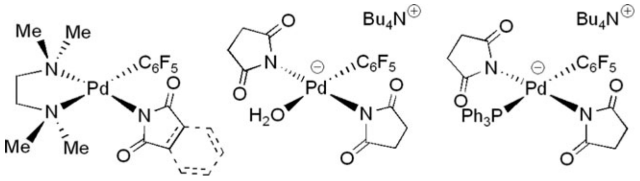


Fig. 8 Neutral and anionic imidate catalysts/precatalysts developed by Ruiz *et al.*.[39]

reactants allows the Pd to be re-used without loss of catalytic activity (over five runs). The importance of precatalyst activation is illustrated by the finding that, provided the initial run was conducted at 90 °C, all subsequent reactions using recycled catalysts could be performed at temperatures as low as 25 °C, without appreciable loss in activity. The thermal stability of the initial precatalyst structures undoubtedly has an impact in these reactions. The Pd species bound to PEO may be "naked" catalysts or "ligand-free".

Interestingly, the catalytic activity of neutral and anionic Pd^{II} complexes containing imidate anions has been reported for Suzuki–Miyaura cross-coupling (Fig. 8).[39]

The catalytic activity (TON $\sim 10^5$–10^6; TON = turnover number defined by mol product/mol catalyst) against activated and deactivated aryl halides is very good and activated aryl chlorides react, which is interesting given the absence of a strongly electron-releasing ligand, *e.g.* $P(t\text{-}Bu)_3$. Some differences in the nature of the imidate were established for the activated substrate, 4-bromoacetophenone. To correlate the imidate effect comprehensively however, further substrates will need to be evaluated.

3.2 Inverse correlation of catalyst loading with catalyst activity

The high conversions seen using 1 mol% of the palladacycles in the Sonogashira cross-coupling of **11** and **12** to give **13** (Scheme 6) led to an investigation into lowering the catalyst loadings in the absence of CuI co-catalyst.[35a] While longer reaction times were anticipated, reactions were deliberately analysed after 6 h, allowing an assessment of any differences in the turnover frequency [TOF, defined by (mol of coupled product) (mol Pd)$^{-1}$ h^{-1}] with catalyst loading to be discerned. This experiment uncovered an exciting observation; the TOF actually increased with lower catalyst loadings (Fig. 9 and Fig. 10).

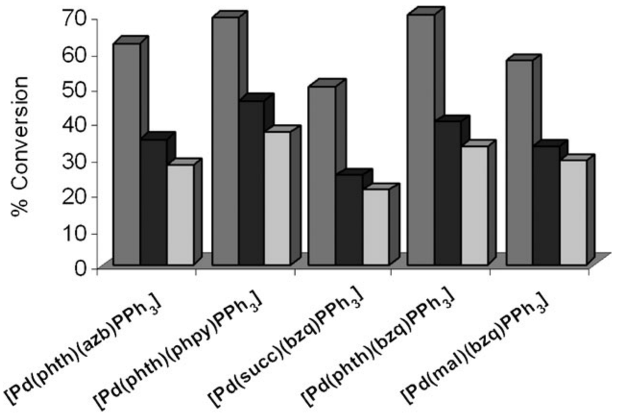


Fig. 9 Sonogashira cross-coupling, in the absence of CuI, of 4-bromoacetophenone **11** with phenylacetylene **12** to give **13** at various Pd catalyst loadings. Reaction time = 6 h, *T* = 100 °C. Key: (▨) (0.1 mol% Pd); (■) (0.01 mol% Pd); (□) (0.001 mol% Pd).

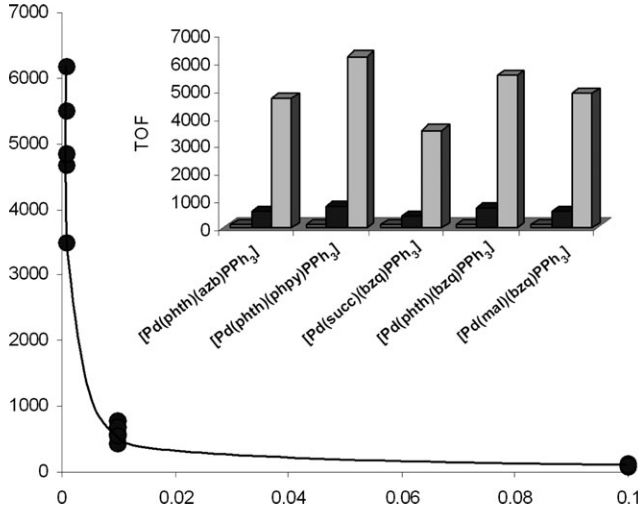


Fig. 10 Graph to show turnover frequency *vs.* Pd loading (defined in text).

Assuming that one 'reactive Pd^0 species' is involved in the reaction, then reducing the catalyst loading from 0.1 to 0.01 mol% should result in a 10-fold decrease in conversion, which turns out not to be the case. Furthermore the difference in conversion after 6 h between 0.01 and 0.001 mol% catalyst loadings was similar ($\sim$3–10%). The turnover numbers increased substantially as the catalyst loading was reduced from 0.1 to 0.001 mol%. Thus, at higher catalyst loadings, the intrinsic catalytic activity is lower, implicating the agglomeration of unreactive Pd^0 clusters. Such clusters could serve as a reservoir for the reactive Pd^0 catalytic species. A similar observation[40] has been made by de Fries *et al.* using low loadings of $Pd(OAc)_2$ in the Heck reaction.[13,14]

Concerning the catalysis studies employing palladacycles based on $[\{Pd(\mu\text{-}NCO)(C^\wedge N)\}_2]$ and $[Pd(C^\wedge N)(imidate)(L)]$ the overall message to convey is that subtle changes to the ligand framework undoubtedly control the formation, propagation and stability of important Pd species within the catalytic cycle(s). It is difficult to deconstruct the complex and interdependent interactions within individual structures. However, through screening a small library of palladacyclic structures, some understanding of the key structural components necessary for higher catalytic activity has been accomplished. Here, the imidate pseudohalides appear to impart different properties.

4 Perspectives

The recent investigations stimulated by the discovery of imidate effects in Pd-catalysed cross-coupling processes triggers new questions concerning the diverse function and role of anionic ligands. It is evident that imidate anionic ligands offer useful and exploitable effects in these reactions. Crucially, mechanistic questions have been raised, leading to the possibility that catalytic cycles other than the standard Pd^0/Pd^{II} version might be operative for some of the Pd complexes described in this perspective. Evidence for the existence of different reaction pathways could ultimately lead to the identification of new transformations, unusual product selectivities and higher reactivity.

In terms of future development, the creation of chiral imidate pseudohalides, for use in asymmetric transition-metal mediated processes, could be an area of potential reward. The possibility to introduce fluorous alkyl chains directly onto the imidate backbone would facilitate efficient removal and recycling of valuable Pd catalysts, as well as other transition-metal catalysts. One can also envisage investigating diverse classes of heterocyclic structures as pseudohalides.

On a general note, a question may be raised about how cross-coupling technology compares against more recently developed synthetic technologies. In Stille coupling, the toxicological effects of Sn are without doubt a limitation for those interested in pharmaceutical design—here other reactions such as Hiyama–Denmark coupling[41] go some way to overcoming this problem. Stille coupling is still a powerful transformation however, and widely used in natural product and materials synthesis. Alkene metathesis[42] on the other hand offers advantages for certain types of alkenyl products over cross-coupling, but certainly not all.[43] C–H activation processes (direct arylation) arguably represent more efficient transformations than classical cross-coupling processes,[44] although it is worth pointing out that the majority of these transformations employ relatively high Pd catalyst loadings (∼5–10 mol% Pd). Interestingly, most of these processes utilise very simple catalyst precursors, *e.g.* $Pd(OAc)_2$. Therefore there are many opportunities to be had in catalyst design in this rapidly emerging area. Here, altering the halide/pseudohalide could have a dramatic affect on reaction efficiency and product selectivity.

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