π-Acidic alkene ligand effects in Pd-catalysed cross-coupling processes: exploiting the interaction of dibenzylidene acetone (dba) and related ligands with Pd(0) and Pd(II)

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π-Acidic alkene (olefin) ligands positively influence Pd-catalysed cross-coupling processes, interacting with both palladium(0) and palladium(II) species, in some cases stabilising key catalytic intermediates. Rates of oxidative addition and reductive elimination are both affected. In certain cases, β-hydrogen elimination can be slowed down by π-acidic alkenes, which opens up new reaction pathways (*e.g.* interception of σ-alkylpalladium(II) species by appropriate nucleophiles). π-Acidic alkene ligands can act independently or in a synergistic fashion with another two-electron donor ligand (*e.g.* amine, phosphine or *N*-heterocyclic carbene). The purpose of this perspective article is to highlight the impressive results that can be obtained using π-acidic alkene ligands, with a particular focus on dibenzylidene acetone (dba) derivatives. Other types of alkene ligands, *e.g.* macrocyclic alkenes, are also discussed.

Introduction

There is significant interest in the application of Pd$^{\circ}$-catalysed cross-coupling processes in drug discovery and complex target-directed synthesis (natural products and advanced materials).[1] Much effort has been placed on the design of strongly activated donor ligands (*e.g.* phosphines and *N*-heterocyclic carbenes) to assist Pd$^{\circ}$ to activate strong C–X bonds in aromatic and related compounds.[2] Furthermore, heteroaromatic substrate scope has been dramatically improved by the use of such ligands. The design of other types of ligands, *e.g.* alkenes, has lagged behind, this despite the established beneficial effects of structurally distinct alkene ligands.[3,4] This can be explained in part by considering the lability of alkene ligands, their chemical conversion and presumed innocence in cross-coupling processes.

The principal aim of this perspective article is to highlight alkene ligand effects in Pd-mediated cross-coupling reactions (and related processes). There is a particular focus on dibenzylidene acetone (dba) type ligands, which is compared, where appropriate, with other alkenes. Before elaborating further it is instructive to consider alkene bonding interactions at both Pd$^{\circ}$ and Pd^{II} centres. Lin and co-workers concluded that the frontier molecular orbital (FMO) interactions involved in alkene binding to Pd$^{\circ}$ and Pd^{II} are distinctly different (Fig. 1).[5] At Pd$^{\circ}$ (strongly π-basic; soft) the alkene ligand predominantly acts as a π-acceptor ligand. At Pd^{II} (weakly π-basic; hard) the alkene ligand acts predominantly as a two-electron π-donor ligand. The binding of non-symmetrical alkenes (*e.g.* terminal alkenes) to Pd is dependent on the nature of the alkene substituent(s). Consideration of the FMOs for π-donor and π-acceptor alkenes allows one to visualise differences in Pd$^{\circ}$ and Pd^{II} alkene complexes: Pd^{II} complexes show non-symmetric alkene coordination, whereas Pd^{0} complexes exhibit near symmetrical alkene coordination.

This outcome can be rationalised by the fact that σ-donation is more important than π-back-donation in the interactions between substituted alkenes and Pd^{II}. In contrast, while π-back-donation plays a dominant role in Pd$^{\circ}$–alkene bonding interactions, σ-donation also plays a principal role. Correlations can be drawn between the dissociation energies and partial charges of the alkene ligands. For Pd^{II}, dissociation energies are greater for those alkenes possessing a π-donating substituent (*e.g.* NMe_2 or OMe). The converse is true for Pd$^{\circ}$ complexes, where the dissociation energies are greater for alkenes bearing a π-accepting substituent (*e.g.* CN). Crucially, for Pd^{II}–alkene complexes there is a linear correlation between alkene partial charge and dissociation energy (as expected for only one dominating bonding interaction), whereas for Pd$^{\circ}$–alkene complexes there is a non-linear correlation (indicating two bonding interactions).

When delineating alkene ligand effects it is instructive to consider alkene substitution reactions by other ligands (*e.g.* O_2,

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Dr Fairlamb is a Royal Society University Research Fellow. Research interests interface through Catalysis, Synthesis and Chemical Biology, particularly in ligand design for Pd catalysts, and an understanding of the reaction mechanisms of cross-coupling processes. The group collaborates extensively with industry (Astra-Zeneca, DSM Pharmaceuticals, GlaxoSmithKline, HemoCORM, Johnson-Matthey and Organon-Schering-Plough).

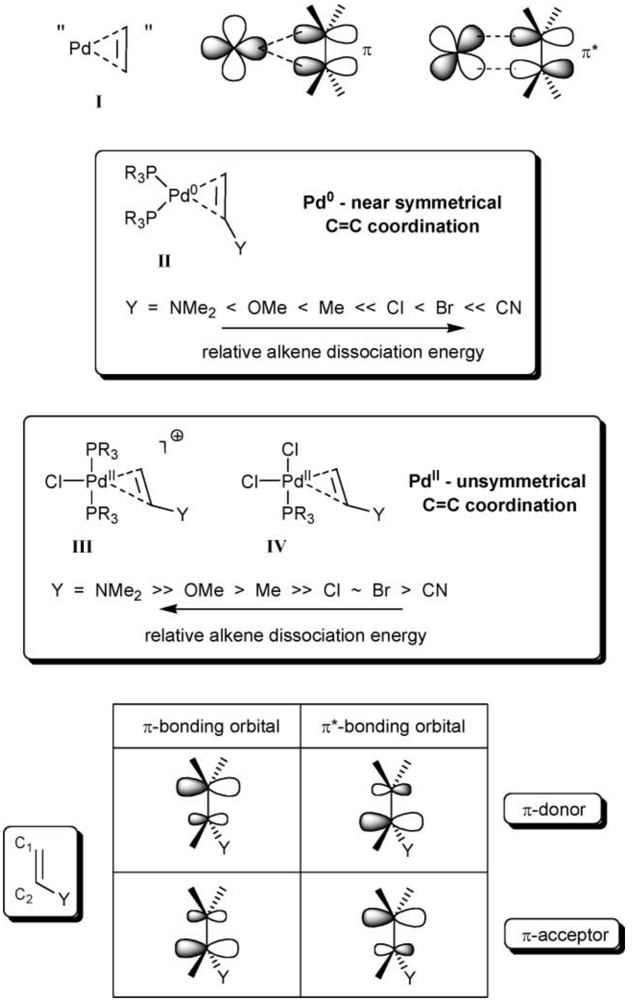
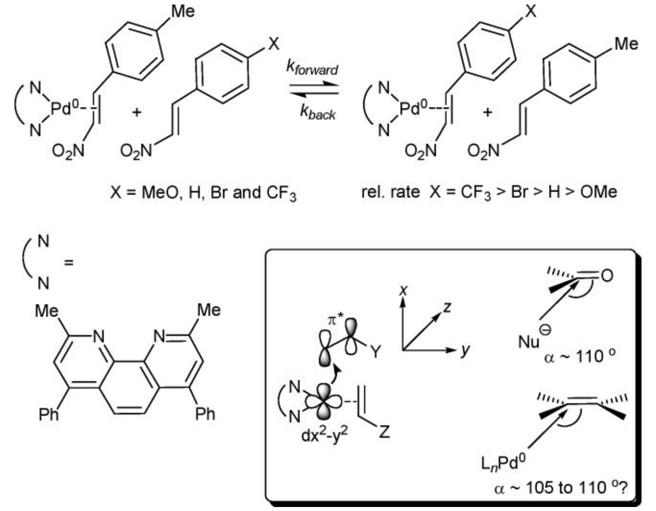


Fig. 1 Relative alkene dissociation energies and molecular orbitals.

CO, CO_2 or a different alkene). Stahl and Landis *et al.* studied the alkene-substitution reactions in a series of bathocuproine–Pd° complexes bearing *trans*-β-nitrostyrene ligands (Scheme 1).[6] Perhaps surprisingly the reactions proceed by an inverse-electron-demand associative mechanism, where a Pd°-based lone pair reacts ($d_{x^2-y^2}$) with the π*-orbital of the incoming alkene. The angle of attack of Pd° to the C=C bond should be near to 105–110°, which can be compared with the Bürgi–Dunitz trajectory[7] (attack of appropriate nucleophile at the π*-orbital of carbonyl groups). Cross-reactions reveal that electron-deficient alkenes react more rapidly than electron-rich (relative) alkenes, *e.g.* the HOMO of the metal and LUMO of the alkene appear to lead the bond forming process.

These findings stand in contrast to traditional ligand-substitution reactions, where the incoming ligand (acting as a nucleophile) donates a pair of electrons to a vacant metal-based orbital. Ligand substitution at Pd° ultimately proceeds by a mechanism resembling oxidative addition (*e.g.* addition of H_2 or RX to M° complexes to give "$M^{II}H_2$" and "$M^{II}RX$", respectively). Thus, there are implications for all electron-rich d^{10} transition metals which activate ligands such as O_2, CO, CO_2 and α,β-unsaturated carbonyl compounds.



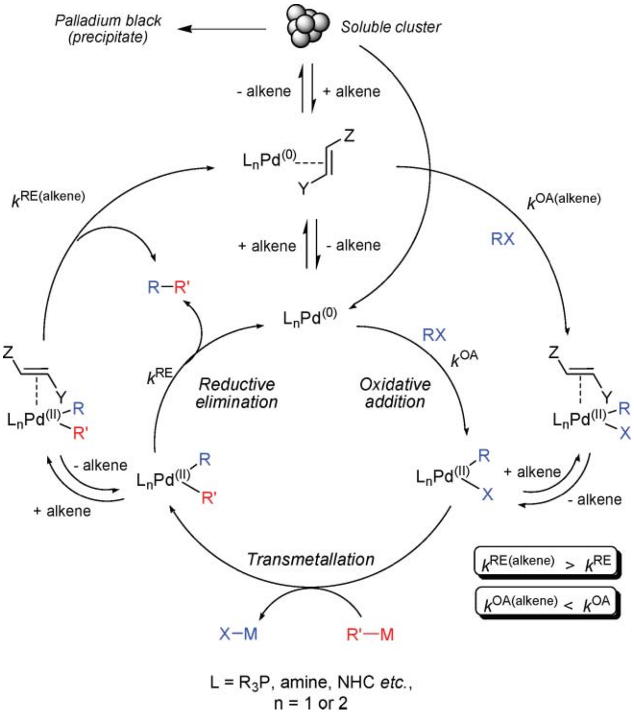
Scheme 1 Alkene exchange in bathocuproine–Pd° complexes bearing *trans*-β-nitrostyrene ligands.

Alkene ligand effects: oxidative addition and reductive elimination

Early on in the development of cross-coupling processes, alkene ligands were found to exert profound effects on elementary steps found in common cross-coupling catalytic cycles. Rovis and Johnson[8] recently covered the effect of these ligands at various transition metals, and prior to analysing the direct effects of such ligands in Pd-catalysed cross-coupling processes, only a brief discussion is given below.

The interaction of alkene ligands[9] in a general cross-coupling catalytic cycle is shown in Scheme 2. Coordination of a π-acidic alkene to Pd° can be viewed as stabilising (towards aggregation and ultimately precipitation), which may affect catalyst longevity *vide infra*. It is established that the rate of oxidative addition of aryl halides to Pd°L_n(η^2-alkene) complexes is slower than to Pd°L_nS complexes (S = solvent; n = 1 or 2).[10] Transmetallation can in principle be assisted by a labile alkene ligand at Pd^{II}; however, it is not yet clear what influence alkenes exert during this step. The rate of reductive elimination will be accelerated by a π-acidic alkene, simply by removing electron-density from Pd^{II}. Furthermore, one could argue that removal of electron-density at Pd° (the 'final' product) provides a thermodynamic driving force.

The mechanistic picture illustrated in Scheme 2 highlights the opportunities for alkene ligand design in general cross-coupling strategies involving Pd° and Pd^{II} intermediates. Furthermore, related processes ought to be influenced where such intermediates are formed, particularly in re-directing β-hydrogen elimination towards cyclisation or in Csp^3-X functionalisation. Given the resurgence of interest in Pd^{IV} coordination chemistry and catalysis,[11] it is worth noting that effects attributable to alkene ligands at this higher oxidation state remain unreported ("η^5-CpPd^{IV}" complexes[12] are known). However, alkene ligation (including substrate activation) at isoelectronic Au^{III} is known,[13] so effects at Pd^{IV} could emerge in the coming years (particularly for π-donor alkenes).



Scheme 2 Alkene effects in a general cross-coupling catalytic cycle.

Non-innocent dibenzylidene acetone (dba-H) ligand effects

A convenient method for generating "$Pd^{\circ}L_n$" complexes *in situ* is to premix a donor ligand (L, *e.g.* PR_3 or *N*-heterocyclic carbene) with the relatively air and moisture stable Pd° precursor complexes, $Pd_2(dba\text{-}H)_3$ or $Pd^{\circ}(dba\text{-}H)_2$ (dba-H = *trans*,*trans*-dibenzylidene acetone[14]). For the vast majority of cases the dba-H ligand[15] remains ligated to Pd° (a phosphole ligand remains the only documented exception[16]). For Pd°, η^2-C=C coordination is most common (Fig. 2, modes **I-III**).[17] Note that intramolecular alkene exchange, *via* C=O coordination, occurs freely in solution for dba-H.[18] For other late metals, *e.g.* Rh^I and Fe°, alternative coordination modes (*e.g.* **IV**[19] and **V**[20]) are well established.

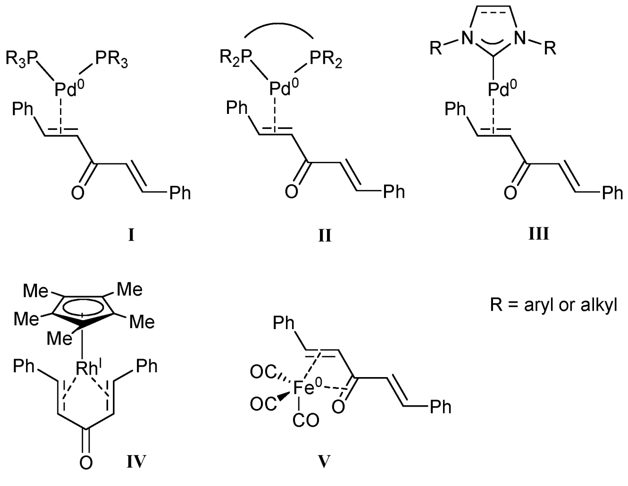
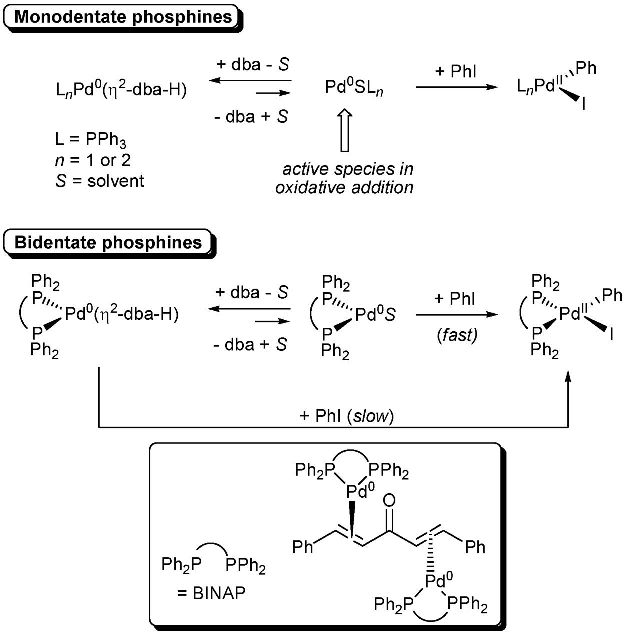


Fig. 2 Coordination modes of dba-H to various metal centres.

With dba-H ligation to Pd° being favoured it is anticipated that the rates of oxidative addition with aryl halides will be affected. In the early 1990s, Amatore and Jutand *et al.* comprehensively studied[21] the non-innocent behaviour of dba-H in the oxidative addition reactions of *in situ* generated $Pd^{\circ}L_n$ species with aryl iodides (Scheme 3). Here, there is an antagonistic effect of the high reactivity of solvated $Pd^{\circ}L_2$ species and its concentration in equilibrium with unreactive $Pd^{\circ}(\eta^2\text{-dba-H})L_2$ species (where L is a monodentate ligand). For more electron-rich donor ligands, *e.g.* *N*-heterocyclic carbenes and phosphines, this emerges as a potential issue. So, whilst electron-rich ligands activate strong C–Cl bonds, dba-H is likely to diminish the concentration of active catalytic $Pd^{\circ}L_n$ species (slowing the rate-determining step for aryl chlorides in cross-couplings). It should be noted, however, that there is limited kinetic data available concerning the reactivity of $Pd^{\circ}(\eta^2\text{-dba-H})L_1$ species in oxidative addition reactions with aryl halides, particularly where L is an electron-rich and sterically hindered *N*-heterocyclic carbene.[22]

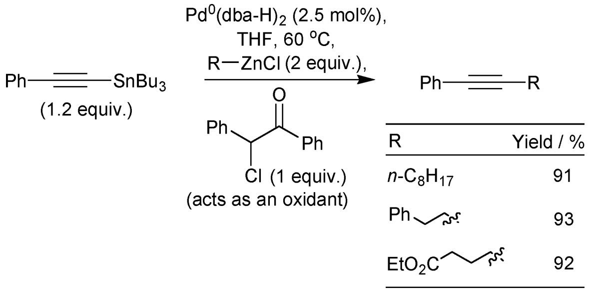


Scheme 3 Ligation of dba-H to Pd° phosphine complexes.

Generally, one could view dba-H ligation to Pd° as a hindrance for both aryl bromides and iodides, *e.g.* oxidative addition being slowed down. However, it serves to bring the rate of oxidative addition in line with the rate of subsequent steps in a catalytic cycle (*e.g.* transmetallation or carbopalladation), lowering the concentration of Pd^{II} species which would otherwise lead to side reactions (*e.g.* homocoupling and hydrodehalogenation *etc.*).[23]

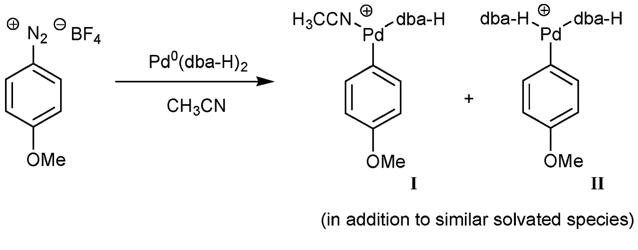
The situation is different for bidentate phosphine ligands, in that oxidative addition of iodobenzene can occur at either $Pd^{\circ}(\eta^2\text{-dba-H})(P\text{-}P)$ or $Pd^{\circ}S(P\text{-}P)$ (S = solvent), but dba-H ligation reduces the reactivity of Pd° – $Pd^{\circ}S(P\text{-}P)$ being more reactive (P-P = BINAP).[24] For BINAP it also worth noting that other "Pd-BINAP–dba-H" complexes[25] can be formed as the concentration of dba-H is lowered, by chemical conversion of dba-H to other products (see inset in Scheme 3).

Whilst more is known about the effects of dba-H on oxidative addition, there are only scattered reports of dba-H enhancing other steps in cross-coupling catalytic cycles. However, an interesting example is the oxidative cross-coupling of alkylzinc and alkynylstannanes using the oxidant, 2-phenyl-2-chloroacetophenone (representative examples are given in Scheme 4).[26] The unexpected rate enhancement of "Csp-Pd-Csp^3" reductive elimination was attributed to dba-H acting as a π-acceptor ligand (removing electron density from the *relatively* electron-rich Pd^{II} centre).



Scheme 4 Oxidative cross-coupling promoted by dba-H.

Well characterised Pd^{II} complexes ligated by dba-H remain rare,[27] but isoelectronic Fe° and Rh^I (*vide supra*) and Ru°–dba-H complexes[28] are known. Interestingly though, dba-H ligation to Pd^{II} has been revealed by ESI-MS experiments,[29] a technique which is particularly useful for characterising transient catalytic reaction intermediates. Eberlin and co-workers were probing the Heck reactions of an aryl diazonium salt, namely 4-MeOC$_6$H$_4$N$_2$$^+BF_4$$^-$, with Pd°(dba-H)$_2$ in acetonitrile. After only 5 minutes, two dba-H ligated Pd^{II} species **I** and **II** were detected (Scheme 5). The dba-H ligation likely aids catalyst stability, carbopalladation rates and β-hydrogen elimination steps. Crucially, this study, and others, highlights that detailed kinetic analyses need to take into consideration the influence of dba-H. Other reactions, *e.g.* allylic alkylation (substitution) processes,[30] are likely affected by the presence of dba-H {Pd°(dba-H)$_2$ is a common Pd° precursor complex for use with chiral ligands in asymmetric allylic alkylations}.[31]



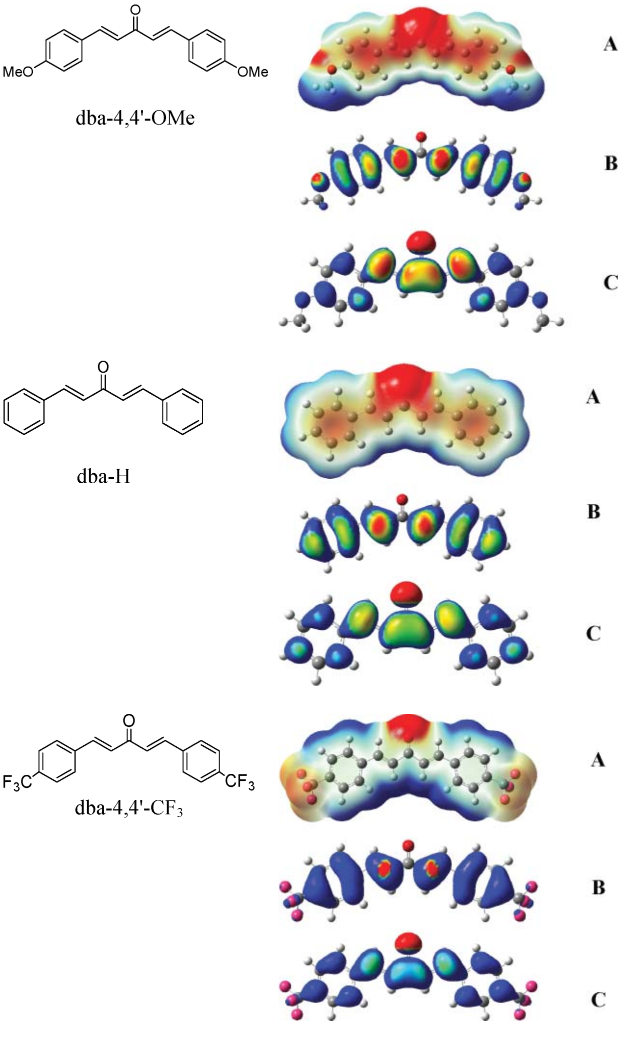
Scheme 5 Detection of Pd^{II}–dba-H species by ESI-MS.

Some unusual effects of Pd°$_n$(dba-H)$_{n+1}$ complexes, as catalyst or catalyst precursor, are often commented upon, particularly in industry, but such effects are not so well documented. From our experience in York, the activity of these complexes tend to slowly degrade over time. The complexes sometimes carry an acetic acid odour, produced by degradation of trace NaOAc, which likely remains from their synthesis, particularly on a large scale. It is not clear whether dba-H {either in free-form or in Pd°$_n$(dba-H)$_{n+1}$} is affected by photooxidation processes[32] in natural light.

Dibenzylidene acetone ligand design

On considering the equilibria depicted in Scheme 3, we developed a ligand design concept based on tuning the C=C bonds in dba-type ligands. One is able to retain the core dba-type structure in tuning the C=C bonds, simply by making remote substituent modifications to the aryl groups (*e.g.* dba-*n*,*n*′-Z; *n*/*n*′ = 3, 4 or 5; Z = OMe, *t*-Bu, Br, H, F, CF$_3$, NO$_2$). It is instructive to consider the calculated total electron densities, HOMOs and LUMOs for several dba-*n*,*n*′-Z ligands (Table 1).[33] These provide an immediate qualitative visualisation of charge variations within the alkene function, which agrees with our intuitive chemical prediction that electron-releasing substituents, *e.g.* OMe, on the aryl groups of dba-type ligands should destabilise the Pd°–alkene interactions, relative to dba-H. Conversely, an electron-withdrawing substituent, *e.g.* CF$_3$, will strengthen any Pd°–alkene interaction. The non-innocent behaviour associated with dba-H,

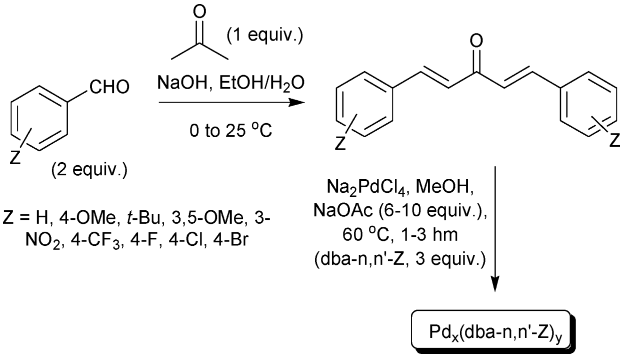
Table 1 Total electron densities, HOMOs and LUMOs for selected dba-*n*,*n*′-Z ligands[a]



[a] Total electron density mapped against electrostatic potentials (A). Colour scale (± 0.02 electrons): red areas are electron-rich. The HOMOs (B) and LUMOs (C) are also shown for each dba-*n*,*n*′-Z ligand.

and the electronic differences between ligands, has thus been exploited in several cross-coupling processes.[34]

In terms of the ligand synthesis, symmetrical[35] and unsymmetrical[36] "dba" structures may be accessed using a number of methods, the most simple of which involves Claisen–Schmidt condensation of two equivalents of the requisite arylaldehyde and acetone (Scheme 6). Various stoichiometries of Pd:dba-*n*,*n*′-Z ligand are produced from these reactions, best determined by elemental analysis. Several Pd°$_x$(dba-*n*,*n*′-Z)$_y$ complexes can be crystallised from $CHCl_3$ or CH_2Cl_2 to give Pd°$_2$(dba-*n*,*n*′-Z)$_3$·solvent (solvent can be subsequently removed *in vacuo*).[37]



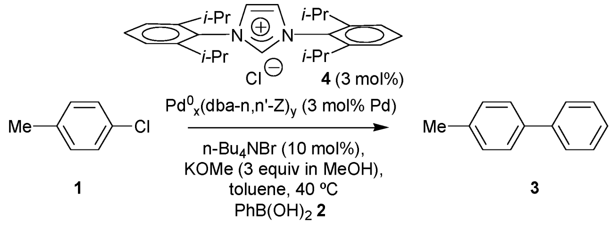
Pd(dba-n,n'-Z)$_2$
[Pd(dba-H)$_2$]
[Pd(dba-3,3',5,5'-OMe)$_2$]
[Pd(dba-4,4'-CF$_3$)$_2$]

Pd$_2$(dba-n,n'-Z)$_3$
[Pd$_2$(dba-H)$_3$]
[Pd$_2$(dba-4,4'-F)$_3$]
[Pd$_2$(dba-4,4'-OMe)$_3$]
[Pd$_2$(dba-4,4'-*t*-Bu)$_3$]
[Pd$_2$(dba-4,4'-CF$_3$)$_3$]
[Pd$_2$(dba-3,3',5,5'-OMe)$_3$

Pd$_2$(dba-n,n'-Z)$_2$
[Pd$_2$(dba-3,3'-NO$_2$)$_2$]

Scheme 6 Synthesis of dba-*n*,*n*′-Z ligands and Pd° complexes.

A series of Pd°$_x$(dba-*n*,*n*′-Z)$_y$ complexes were benchmarked in Suzuki–Miyaura cross-couplings using aryl chlorides as a stern test (Scheme 7). The reaction of chlorotoluene **1** with phenylboronic acid **2**, reported to be catalyzed by Pd°$_2$(dba-4,4′-H)$_3$ (3 mol %)/NHC ligand (derived from imidazolium salt **4**) (3 mol %), affords **3**. The major outcome is that more electron-rich Pd°$_x$(dba-*n*,*n*′-Z)$_y$ complexes give high rates and conversions to **3**. A rate-determining oxidation addition is thus implied by these findings. A Hammett plot, utilising σ^+ values, exhibits a linear trend for the *para*-substituted Pd°$_2$(dba-4,4′-Z)$_3$ complexes (Z = OMe, *t*-Bu, H, F or CF_3). An excellent correlation is also seen between the rates and the calculated C=C charge in the dba-4,4′-Z ligands.[33] Furthermore, related chalcone (p-Z-C_6H_4CH=CHPh) ligands show similar electronic effects at Fe°,[38] demonstrating that such ligands[39] could be used in the future to influence steps in classical cross-coupling processes.

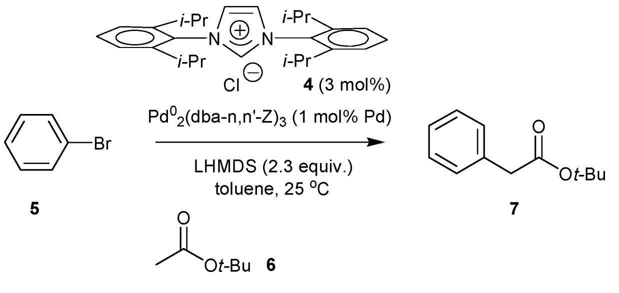


Relative rate (consumption of ArCl)

Pd^0(dba-n,n'-Z)$_2$	3,3',5,5'-OMe > H > 4,4'-CF$_3$
Pd$^0_2$(dba-n,n'-Z)$_3$	4,4'-OMe > 4,4'-*t*-Bu ~ H ~ 4,4'-F > 4,4'-CF$_3$

Scheme 7 Suzuki–Miyaura cross-coupling.

In an alternative cross-coupling, namely the α-arylation of *t*-butyl acetate **6** with bromobenzene **5** using LHMDS as the base to give the α-arylated product **7**, a similar trend in reactivity for Pd°$_2$(dba-*n*,*n*′-Z)$_3$ precatalysts was revealed (Scheme 8).[34c]



Relative rate (consumption of ArBr)

3,3',5,5'-OMe > 4,4'-OMe > 4,4'-*t*-Bu ~ H ~ 4,4'-F > 4,4'-CF$_3$

Scheme 8 α-Arylation of esters.

Heck arylations emphasise that dba-*n*,*n*′-Z ligands compete with the alkene substrate, particularly with *n*-butyl acrylate (Fig. 3). The extent of 'dba-*n*,*n*′-Z participation' is diminished on switching to styrene and methyl 2-acetamido acrylate substrates. It is therefore

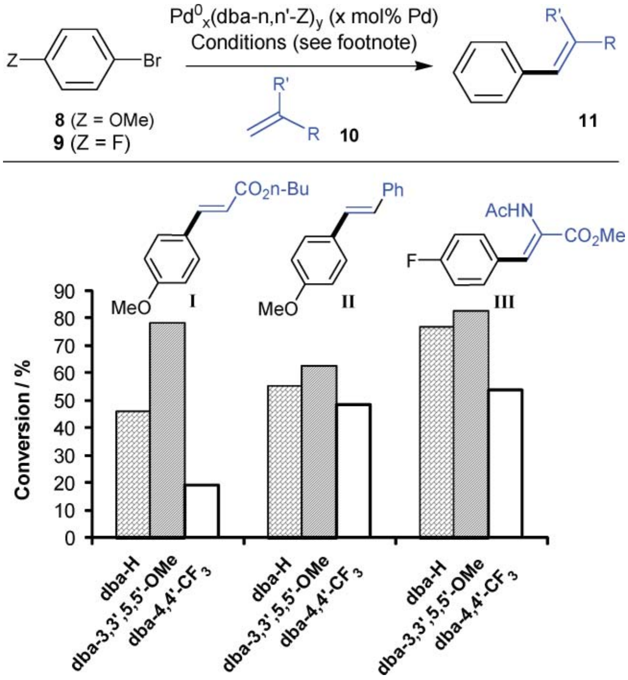
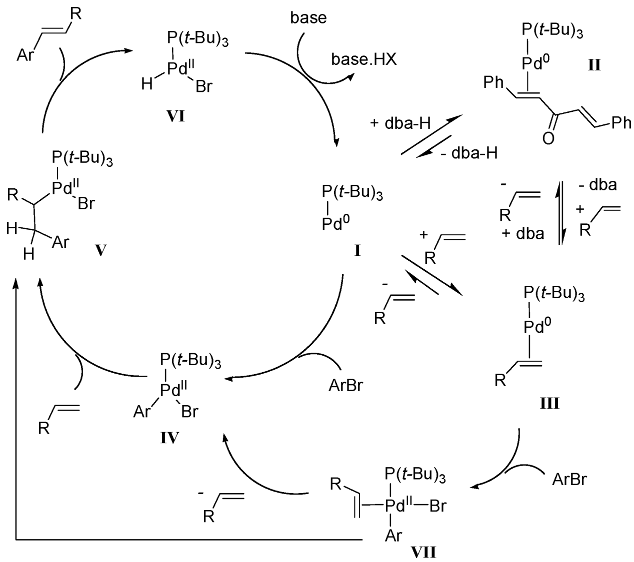


Fig. 3 Heck arylation of various *n*-butyl acrylates, styrenes and methyl 2-acetamido acrylates. Conditions used: (reactions I and II) Pd°$_2$(dba-4,4′-Z)$_3$ (3 mol% Pd), P(*t*-Bu)$_3$·HF_4 (3.6 mol%), Cs_2CO_3, dioxane, 100 °C, 12 h; (reaction III) Pd°$_2$(dba-4,4′-Z)$_3$ (0.3 mol% Pd), $BnNEt_3Br$, (*i*-Pr)$_2$Net, NMP, 125 °C, 3 h.

important to consider the electronic character of the alkene coupling partner in these reactions, with electron-rich or sterically demanding alkenes being more affected by dba-*n*,*n*′-Z ligands than electron-deficient alkenes.[34c]

The mechanism outlined in Scheme 9 illustrates the roles of the alkene ligands in the catalytic cycle. The reactive Pd species **I** (solvated) is assumed to be monoligated by P(*t*-Bu)$_3$, the concentration of which will be diminished by both the dba-*n*,*n*′-Z ligand and alkene substrate, to give **II** and **III**. The concentration of **II** and **III** will be governed by the strength of alkene interaction with Pd°. Crucially, for mono-phosphine ligated species **III**, direct oxidative addition gives complex **VII**, which can either undergo carbopalladation to give **V** or alkene ligand loss to give **IV**. For styrene and methyl 2-acetamido acrylate, the relative conversions indicate that there is a delicate balance between the equilibria of **I** and **II** and **I** and **III** (**II** and **III** also being in equilibrium). To maximise a dba-*n*,*n*′-Z ligand effect, the alkene substrate needs to be carefully considered.



Scheme 9 Competing alkene ligands in Heck arylation.

For most Buchwald–Hartwig type aryl amination processes, there is no real advantage in employing the Pd°$_x$(dba-*n*,*n*′-Z)$_y$ complexes. Here the dba-*n*,*n*′-Z ligands can be consumed by amine, base or a combination of both.[25] Indeed, for the majority of these aryl amination reactions, Pd(OAc)$_2$ is arguably the preferred palladium source (precatalyst).

In developing the tuneable dba-*n*,*n*′-Z ligand concept, the theoretical calculations[33] allowed a linear relationship to be discerned between the calculated carbonyl stretching frequency (bond strength) for each dba-*n*,*n*′-Z ligand (in the gas-phase) and the associated rates determined for aryl halide consumption in the Suzuki–Miyaura, α-arylation and Heck arylation reactions detailed above (Fig. 4). This offers a simple but rapid experimental tool for verifying the electronic properties of future, new dba-*n*,*n*′-Z ligand variants, as expressed in the equation below.

$$k' = (-4.039 \times 10^{-6}\ \upsilon_{C=O}) + 7.045 \times 10^{-3}$$

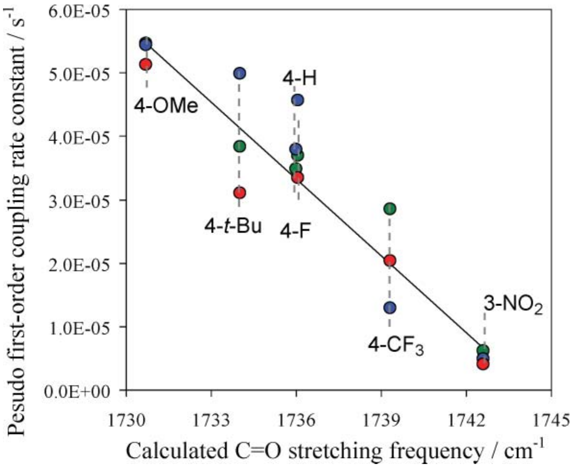
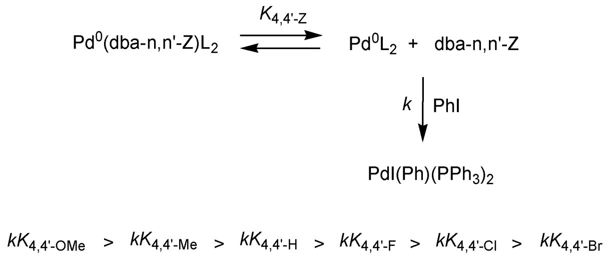


Fig. 4 Relationship of C=O stretching frequency in dba-*n*,*n*′-Z ligands with rates of aryl halide consumption (green circles = Suzuki–Miyaura cross-coupling; blue circles = α-arylation; red circles = Heck arylation).

Kinetic studies: reactivity of Pd° complexes generated from Pd°$_2$(dba-*n*,*n*′-Z)$_3$ or Pd°(dba-*n*,*n*′-Z)$_2$ and PPh$_3$ in oxidative addition with iodobenzene

In collaboration with Jutand, we have been able to establish that the rate of the oxidative addition of iodobenzene to "Pd°L(PPh$_3$)$_2$" (L = solvent or dba-*n*,*n*′-Z) complexes, generated by addition of PPh$_3$ (PPh$_3$/Pd = 2) to DMF, was affected by the electron-donating or accepting properties of Z substituents attached to the aryl groups of the dba motif.[34b]

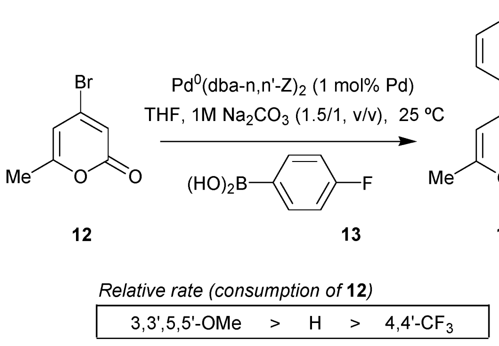
The rate of oxidative addition is faster when Z is an electron-donating group.[40] The dba-*n*,*n*′-Z ligand plays a crucial role in the kinetics of oxidative additions by controlling the concentration of the reactive Pd°(PPh$_3$)$_2$ in its equilibrium with the major but unreactive complex Pd°(η^2-dba-*n*,*n*′-Z)(PPh$_3$)$_2$ (equilibrium constant K_Z in Scheme 10). As the Z group becomes more electron-releasing, there is a lower affinity of dba-*n*,*n*′-Z for the electron rich Pd°(PPh$_3$)$_2$. Therefore K_Z is higher and oxidative addition is faster. Consequently, the rate of oxidative additions is modulated by altering the electronic properties of the dba-*n*,*n*′-Z ligands.



Scheme 10 Effect of dba-*n*,*n*′-Z ligands on the rate of oxidative addition of PhI to "Pd°(PPh$_3$)$_2$" species.

The order of reactivity of dba-4,4′-X ligands (F > Cl > Br; X = halogen) highlights that π-donor effects dominate over σ-electron-withdrawing effects, a trend also seen in BX$_3$ Lewis acidities.[41]

Under 'ligand-free' reactions, loosely defined as those which do not require additional phosphine (*e.g.* a strong 2-electron donor ligand), cross-coupling of a halogenated 2-pyrone **12** with arylboronic acid **13** to give **14**, a dba-*n*,*n*′-Z ligand effect was uncovered (Scheme 11). Addition of PPh_3 slows down this particular reaction. The degree of nakedness of the Pd° catalyst is debatable, but one can envisage that dba-*n*,*n*′-Z ligands influence both mononuclear {*e.g.* PdS_n(dba-*n*,*n*′-Z)$_{n-1}$} and higher order Pd species (*e.g.* clusters/colloids/nanoparticles) *vide infra.*

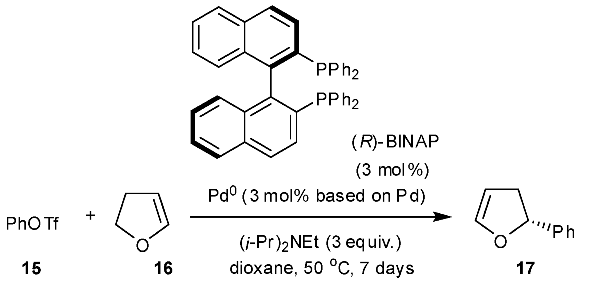


Scheme 11 Suzuki–Miyaura cross-couplings under phosphine-free conditions.

Catalyst longevity is important in the intermolecular asymmetric Heck reaction of 2,3-dihydrofuran **16** with phenyltriflate **15** to give **17**, which are generally very slow processes (*ca.* 7 days). It has been established that $Pd°_2$(dba-4,4′-F)$_3$ was the most effective Pd° precursor complex using (*R*)-BINAP as the chiral ligand (Table 2). Whilst the enantioselectivity for the major regioisomeric product was near identical to $Pd°_2$(dba-H)$_3$, the overall conversion was significantly higher. The long reaction time (7 days) appears to benefit from a Pd° catalyst that is long-lived, dba-4,4′-F being more electron-deficient than dba-H.[34b] Alternatively, 2,3-dihydrofuran **16** may compete effectively with the dba-4,4′-F ligand (at Pd^{II}).

Pregosin and co-workers showed that dba-H slows/inhibits catalytic turnover in the same asymmetric Heck reaction using MeO-Biphep ligand **18** under similar reaction conditions (Fig. 5).[42] The catalyst generated from $PdCl_2$(**18**)–$NaBH_4$ was found to be active for this reaction, however Pd(η^2-dba-H)(**18**) was not. In addition, Pd(η^2-dba-H)(**18**) does not react even with activated aryl halides (*e.g.* iodobenzene). Clearly dba-H ligation *in this case* reduces the nucleophilicity of the Pd° centre (*via* π-back-bonding—a resonance structure[43] for this complex would go some way to explaining its apparent lack of reactivity towards activated aryl halides). It ought to be borne in mind that the borohydride reduction route affords chloride ions, which can lead to more electron-rich Pd° anions being generated under the reaction conditions (*e.g.* $PdCl_x$(**18**)$_{x-1}$ ($x = 1$ or 2). The cautionary message here is that for certain bidentate phosphine ligands, dba-H can hinder catalysis.

Table 2 Heck reaction of 2,3-dihydrofuran with phenyltriflate



Pd° Precursor $Pd°_2$(dba-4,4′-Z)$_3$	Yield (%)[a]	e.e. (%)[b]
H	51	63
CF_3	42	61
F	69	68
OMe	63	62

[a] Percentage yield after column chromatography on silica-gel (average of at least two runs). [b] The enantiomeric excess (e.e.) was determined on a β-cyclodextrin chiral column by GC.

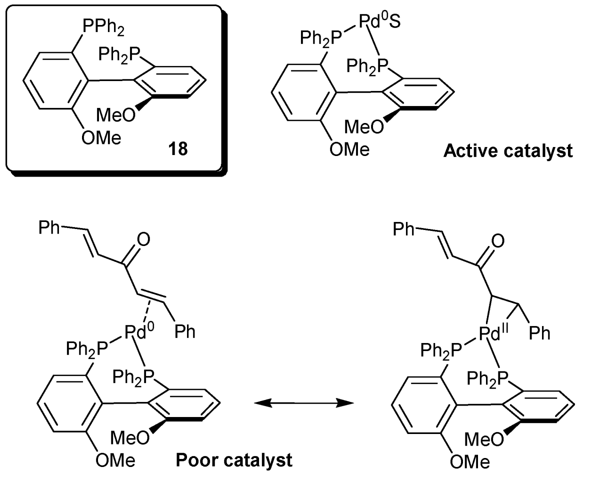
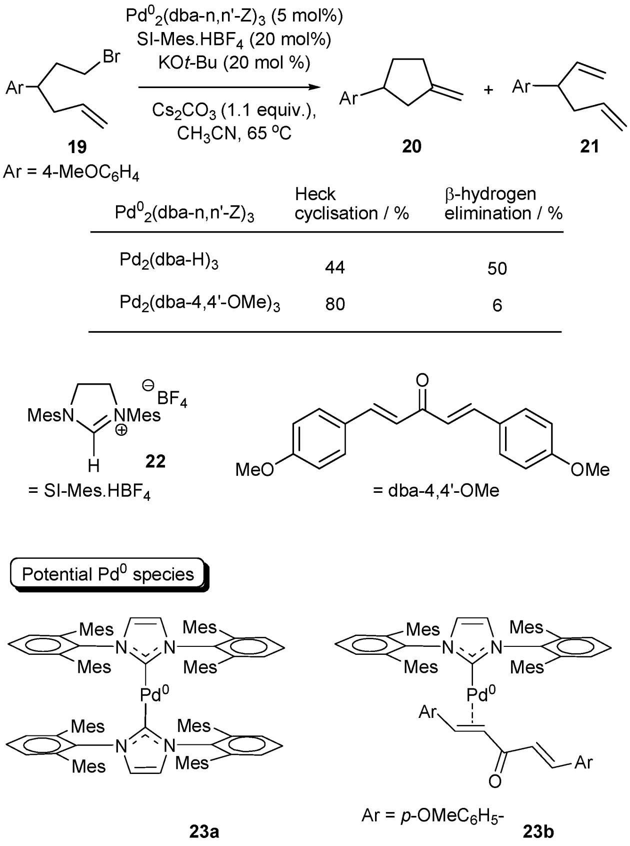


Fig. 5 The case against dba-H.

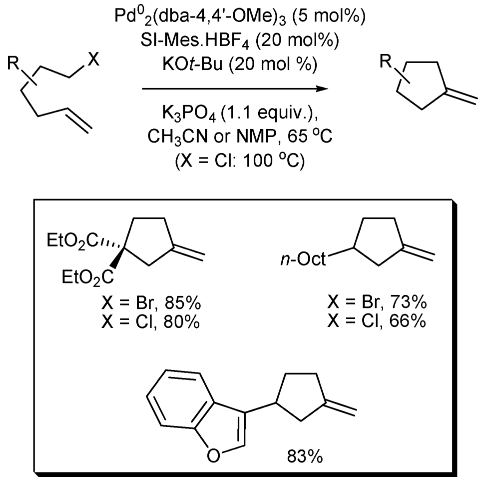
Firmansjah and Fu recently reported intramolecular Heck reactions of unactivated alkyl halides, which showed a remarkable dba-effect.[44] Generally, oxidative addition of alkyl bromides to Pd°L_n is a feasible process, but β-hydrogen elimination from the resultant "Pd^{II}(σ-alkyl)Br" intermediate species usually reveals a terminal alkene and "Pd^{II}(H)Br", making intermolecular Heck reaction processes difficult to develop. However, the intramolecular Heck reaction of a primary alkyl bromide **19** possessing a pendant alkene, mediated by a $Pd°_2$(dba-H)$_3$–NHC catalyst system, which likely generates **23a**[45] or **23b**[34c] as Pd° intermediates, highlights that cyclisation to give **20** is possible (Scheme 12). Perhaps the β-hydrogen elimination 1,5-diene side-product **21** is to be expected, being an equi-competitive path. It is then quite remarkable that the use of $Pd°_2$(dba-4,4′-OMe)$_3$ as the palladium source resulted in cyclisation becoming the dominant reaction pathway. The substrate scope in these reactions is very good, and both alkyl bromides and chlorides participate well (Scheme 13). There is thus much potential for this methodology to be applied in target-orientated synthesis.

It can be hypothesised that dba-4,4′-OMe slows down β-hydrogen elimination from the "Pd^{II}(σ-alkyl)Br" oxidative addition species (as proposed in **I**, Fig. 6), allowing carbopalladation (cyclisation) to take place; note that β-hydrogen elimination in **II**, a three-coordinate Pd^{II} species, would be facile, giving the 1,5-diene side-product (*e.g.* **21**). β-Hydrogen elimination from a cyclic σ-alkylpalladium(II) intermediate, possessing less conformational freedom, must occur with the dba-4,4′-OMe ligand present. Relative to dba-H, dba-4,4′-OMe is more electron-rich, preferring Pd^{II} to Pd°.



Pd^0_2(dba-n,n'-Z)$_3$	Heck cyclisation / %	β-hydrogen elimination / %
Pd_2(dba-H)$_3$	44	50
Pd_2(dba-4,4'-OMe)$_3$	80	6

Scheme 12 Redirecting β-hydrogen elimination at Pd^{II}.



Scheme 13 Substrate scope (representative examples).

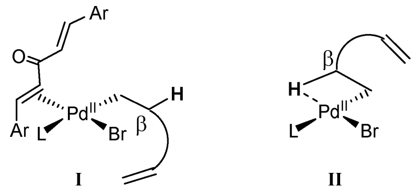
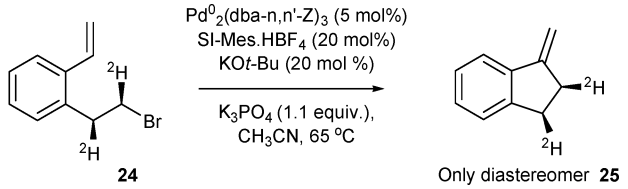


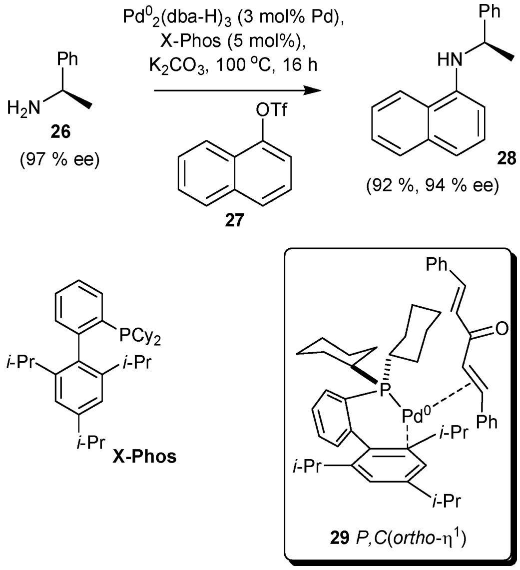
Fig. 6 Hindering β-hydrogen elimination.

On probing the reaction mechanism, it was elegantly shown that cyclisation of deuterium-labelled substrate **24** affords a single diastereomer **25**, the stereochemistry of which is consistent with oxidative addition occurring in an S_N2 fashion, *e.g.* the reaction does not proceed through a radical pathway (Scheme 14).[44]



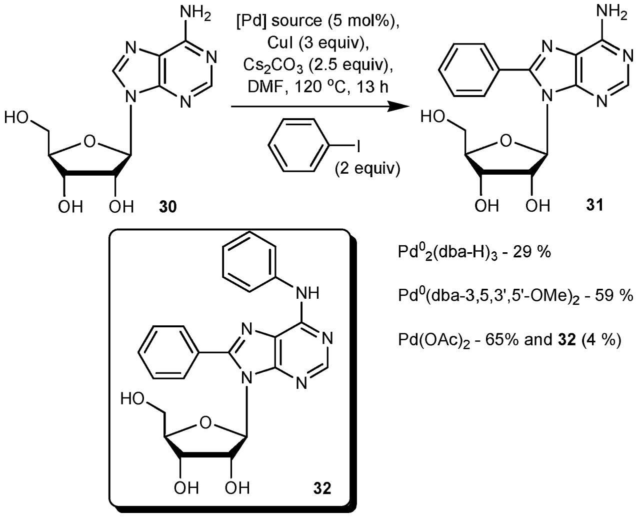
Scheme 14 Probing a radical pathway.

Meadows and Woodward reported that a catalyst composed of X-Phos–Pd°_2(dba-H)$_3$ was optimal for the model reaction of aryl triflates (on nonaflates) with benzyl amine.[46] Crucially, Pd°_2(dba-H)$_3$ is uniquely superior to Pd(OAc)$_2$. Substituting the amine for chiral (*R*)-PhCH(Me)NH$_2$ **26** in a reaction with naphthyl triflate **27** to give **28** led to only small degrees of racemisation (Scheme 15). It is proposed that X-Phos does not act as a simple monodentate phosphine, which likely adopts a *P*,*C*=*C* chelate bidentate binding mode (as in **29**),[47] which slows down β-hydride elimination, a prerequisite for amine racemisation. It is also possible that dba-H plays a similar role, akin to that observed in the intramolecular Heck reactions of unactivated alkyl halides *vide supra.*

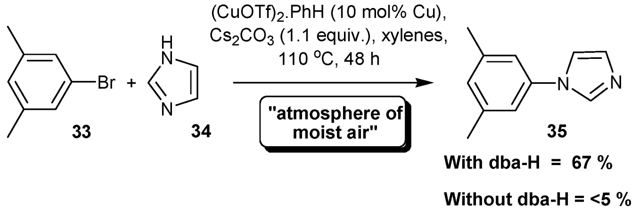


Scheme 15 Aryl amination of chiral amines.

The Pd-catalysed arylation of adenosine in the presence of stoichiometric CuI reveals that Pd°(dba-3,5,3′,5′-OMe)$_2$ is a more active Pd source than Pd°(dba-H)$_2$ (Scheme 16).[48] Whilst Pd(OAc)$_2$ exhibits similar activity to Pd°(dba-3,5,3′,5′-OMe)$_2$, it is interesting to note that the dba-*n*,*n*′-Z ligands appear to hinder *N*-arylation.[49] The beneficial effect of dba-H in the copper-catalyzed *N*-arylation of imidazoles using (CuOTf)$_2$, reported by Buchwald and co-workers, is certainly worth mentioning here (Scheme 17).[50] It was proposed that dba-H (5 mol%) prevents disproportionation to give Cu° or Cu^{II} species, a particular problem running the reactions under ambient conditions. Alternatively, the dba-H ligand could stabilise the catalytically active Cu^I species. There is possibly an opportunity here for exploiting the differential reactivity of dba-*n*,*n*′-Z ligands in these reactions.



Scheme 16 Direct arylation of adenosine.



Scheme 17 A dba-H effect in copper-catalyzed *N*-arylation.

Other alkene ligands[8]

Moreno-Mañas, Pleixats, Roglans and co-workers[51] have developed macrocyclic trialkene ligands (*e.g.* **36** and **37**) for Pd° over the last five or so years (Fig. 7). The Pd° complexes containing these ligands provide a more stable ligand environment than, for example that offered by the three alkene ligands in Pd°(dba-H)$_3$ **38**. The ferrocenyl group(s) in macrocyclic ligand **36** (and **37**) appear to strongly influence the Pd(0) redox properties,[52] perhaps in a mode similar to 1,1′-bis(diphenylphosphino)ferrocene (dppf).[53]

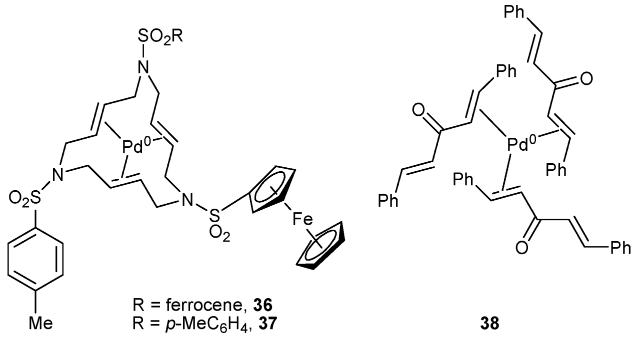
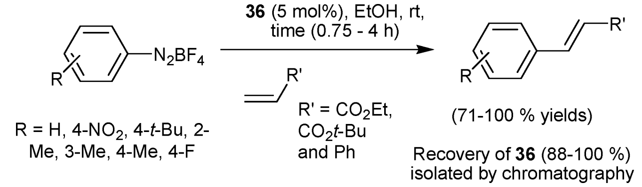


Fig. 7 Macrocyclic trialkene Pd° complexes.

The Heck arylation reactions of aryl diazonium salts are effectively mediated by recoverable catalyst **36** at room temperature (Scheme 18).[54] In contrast to aryl bromides and iodides, oxidative addition is not thought to be rate-limiting for aryl diazonium salts and a superior activity of the nucleofuge (formation of N$_2$) is expected over both bromide and iodide ions.



Scheme 18 Heck arylation using aryl diazonium salts.

Electrospray-mass spectrometric studies provided evidence for the accumulation of the oxidative addition species ([**36**/C$_6$H$_4$R]$^+$, where R = H, $m/z = 946$; R = 4-NO$_2$, $m/z = 991$; R = 4-Me, $m/z = 960$; R = 4-F, $m/z = 964$) formed in the catalytic cycle immediately before the alkene insertion step. Similar intermediates were observed for dba-H ligands by Eberlin and co-workers[29] *vide supra.* On addition of alkene to these reactions, no transient alkene insertion intermediates were detected. However, the detection of oxidative addition intermediates ligated by alkene ligand once again highlights the potential for alkene tuning.

The catalytic activity of many Pd° complexes containing macrocyclic alkene ligands has been reported: selected examples (**39** and **40**, Fig. 8) are described here.

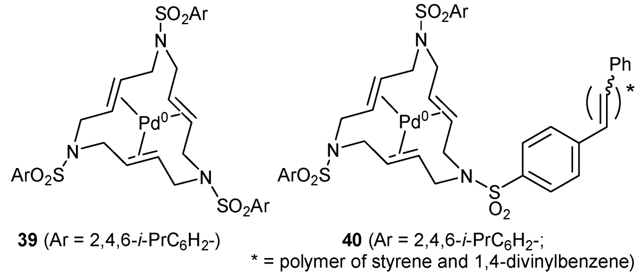
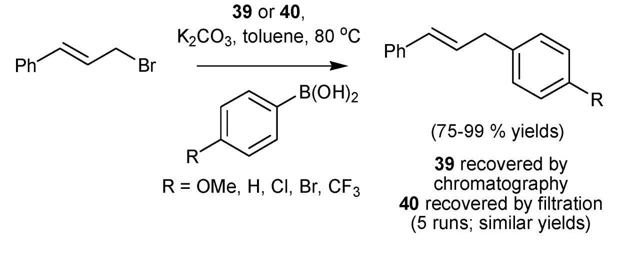


Fig. 8 Macrocyclic trisalkene Pd° catalysts.

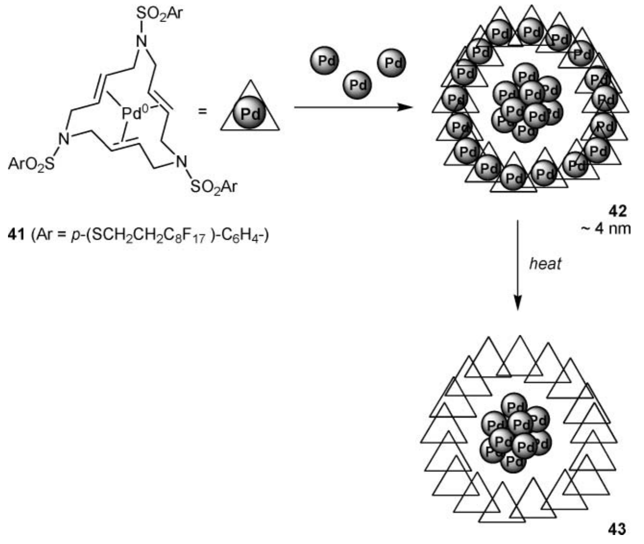
Complex **39** is an effective catalyst for Suzuki–Miyaura cross-coupling[55] (Scheme 19), which is also recoverable by chromatography on silica-gel. The polymeric variant **40** is equally effective at catalysing this reaction—similar yields and five runs were possible using this easily separated palladium catalyst.



Scheme 19 Macrocyclic trisalkene Pd^0 catalysts in Suzuki–Miyaura cross-coupling.

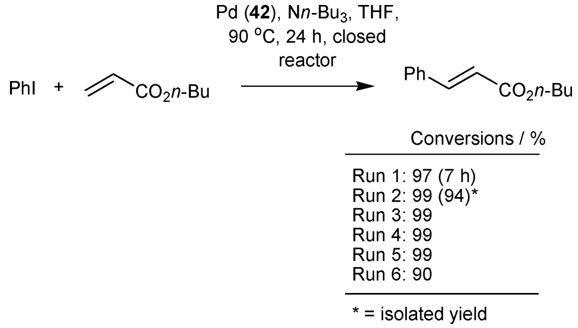
Structurally defined Pd nanoparticles can be generally useful catalytic palladium sources for cross-coupling processes, mainly due to their high specific surface area.[56] Several macrocyclic alkene Pd° complexes (*e.g.* **41**) have been shown to form Pd nanoparticles **42** when treated with excess Pd° (Scheme 20).[57]

Heating **42** in THF results in the loss of Pd from the periphery of the nanoparticle, resulting in stabilisation of an inner core of Pd° atoms by the alkene ligand, giving **43**. This process is likely mirrored in catalytic reactions heated to higher temperatures.



Scheme 20 Aggregation of macrocyclic-Pd° complexes.

It was shown that **42** is an effective reusable Pd° catalyst for Heck arylation of *n*-butyl acrylate with iodobenzene (Scheme 21). For highly activated substrates, it is advantageous to use high substrate : Pd ratios. In the case of **42**, the alkene ligand(s) serves to stabilise a Pd°-reservoir,[56] trickle-feeding[58] in low concentrations of highly active mononuclear Pd° species.



Scheme 21 Heck arylation using Pd nanoparticles **42**.

Moreno-Mañas and co-workers have also prepared Pd nanoparticles (**45**) stabilised by "fluorous-dba" **44**, which are 4–5 nm in diameter (Fig. 9).[59] In a near identical reaction to that shown in Scheme 19, in a perfluoroctylbromide–benzene solvent, similar product yields, recovery of catalyst and reusability was found for these Pd nanoparticles. These studies show that dba-type ligands can also stabilise Pd nanoparticles.

Kinetic studies: reactivity of Pd° complexes generated from Pd°(46) and PR$_3$ in oxidative addition with aryl halides

Jutand and Pleixats investigated the reaction kinetics (monitored by electrochemical techniques) of oxidative addition of aryl halides (PhI and PhBr) to Pd° complexes generated *in situ* from Pd°(**46**) and monophosphines L (L = PPh$_3$ and PnBu$_3$) in THF or DMF (Fig. 10).[60]

The macrocyclic ligand **46** was shown to play an important role in diminishing the concentration of the most reactive catalytic Pd°L$_2$ species in oxidative addition (as stated in Scheme 3).

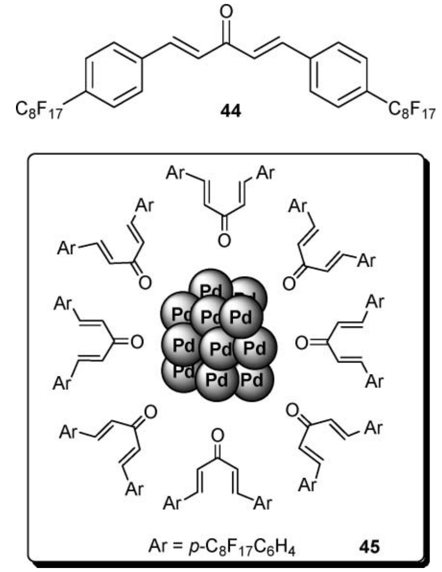


Fig. 9 Pd nanoparticles stabilised by fluorous-dba.

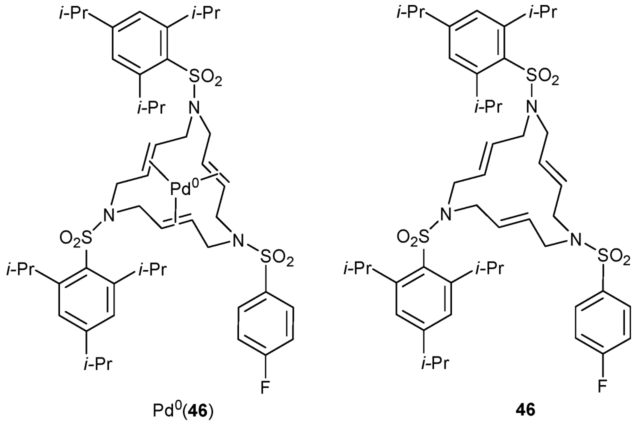
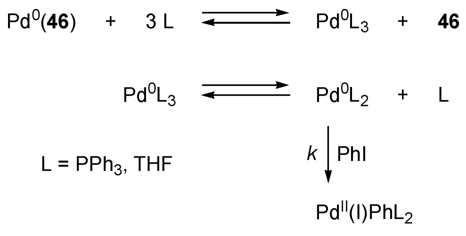


Fig. 10

A reactivity order with PhI was established as:

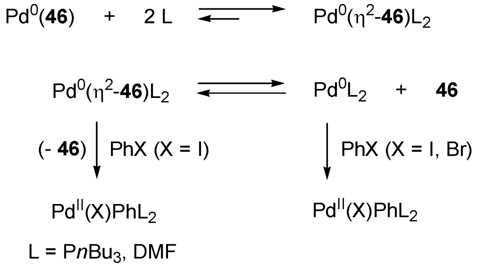
Pd°(**46**) + 2 PnBu$_3$ in DMF > Pd°(**46**) + 2 PPh$_3$ in THF > Pd°(PPh$_3$)$_4$ in THF > Pd°(**46**) + 4 PPh$_3$ in THF

For PPh$_3$, ligand **46** is in equilibrium with Pd°(PPh$_3$)$_2$ *via* Pd°(PPh$_3$)$_3$, whose concentrations are controlled by the concentration of **46** (Scheme 22).



Scheme 22

It is interesting to note that addition of n (>2) equivalents of PnBu$_3$ to Pd°(**46**) in DMF leads to the formation of both Pd°(η^2-**46**)(PnBu$_3$)$_2$ and Pd°(PnBu$_3$)$_3$, which were characterised by ^{31}P NMR spectroscopy (Scheme 23). At equal phosphine–Pd loading, the Pd° complexes generated by addition of PnBu$_3$ to Pd°(**46**)



Scheme 23

are more reactive than that ligated by PPh$_3$, allowing reaction of PhBr at 25 °C. The rate of oxidative addition of PhBr (at high concentration) was found to be limited by dissociation of Pd°(P*n*Bu$_3$)$_2$ from Pd°(η^2-**46**)(P*n*Bu$_3$)$_2$. Furthermore, the reaction with PhI was found to also involve Pd°(η^2-**46**)(P*n*Bu$_3$)$_2$ as the reactive species.

The global point, as was the case for the dba-*n*,*n*′-Z ligands, is that the decelerating effect induced by **46** is useful where oxidative addition is fast, since slowing this step brings its rate nearer to the rate of the subsequent step which is slower (*e.g.*, transmetalation or carbopalladation). Ligand **46** also serves to stabilise Pd°, improving catalyst longevity.

Future perspectives

From the results detailed in this perspective article, and other recent review articles in this area,[3,61] there can be no doubt that alkene ligands offer much potential in terms of opening up new reaction pathways or simply improving the general efficacy of cross-coupling processes. Pd°-complexes possessing dba-*n*,*n*′-Z ligands can be used for a raft of Pd-catalysed coupling processes and it is anticipated that new practical methodologies will emerge over the coming years. One practical issue that emerges for dba-*n*,*n*′-Z, and related ligands, is that the polarity of these ligands is often similar to the organic products being produced. Whilst fluorous-dba type ligands go some way to addressing this issue, it would be useful to prepare alkene ligands that can be tuned to increase catalyst efficacy, which can subsequently be easily separated (and recycled) from the desired organic product (avoiding column chromatography on silica-gel). A potential ligand system would be one possessing a suitable π-acidic ligand tethered to an ionic arm, which could be easily dosed into compatible ionic liquids (IL), *e.g.* [BMIM]PF$_6$. The products could then be extracted from the IL–catalyst–ligand mixture using a suitable solvent or by utilising the low vapour pressures of ILs to separate the products using vacuum distillation. Such catalyst-doped ILs have significant potential for recycling and re-use.

Acknowledgements

I am grateful to all the people who have contributed to developing the dba-*n*,*n*′-Z ligand concept, particularly Drs A. R. Kapdi and G. P. McGlacken. This, and related, work has greatly benefited from collaboration with Professor A. Jutand (Ecole Polytechnique, Paris), Dr A. F. Lee (York), Dr A. H. M. De Vries (DSM pharmaceuticals) and Professor Z. Lin (Hong Kong University of Science of Technology). I thank them for their considerable input into this project. Professor G. C. Fu (M.I.T.) is thanked for a paper pre-print[44] and further helpful discussions. Finally, I would like to thank Drs J. M. Lynam and J. Slattery (York) and Professor T. B. Marder (University of Durham) for many stimulating discussions regarding this area of ligand design.

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