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Exploiting Noninnocent (*E*,*E*)-Dibenzylideneacetone (dba) Effects in Palladium(0)-Mediated Cross-Coupling Reactions: Modulation of the Electronic Properties of dba Affects Catalyst Activity and Stability in Ligand and Ligand-Free Reaction Systems

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Abstract: The reactivity of palladium(0) complexes, $[Pd^0_2(dba\text{-}n,n'\text{-}Z)_3]$ (n,n'-Z = 4,4′-F; 4,4′-CF_3; 4,4′-H; 4,4′-MeO) and $[Pd^0(dba\text{-}n,n'\text{-}Z)_2]$ (n,n'-Z = 4,4′-CF_3; 4,4′-H; 3,3′,5,5′-OMe), used as precursor catalysts with suitable donor ligands (e.g. phosphines, N-heterocyclic carbenes), has been correlated in several palladium(0)-mediated cross-coupling processes. Increasing the electron density on the aryl moiety of the dba-*n*,*n*′-Z ligand increases the overall catalytic activity in the majority of these processes. This effect primarily derives from destabilization of the L_nPd^0–η^2-dba interaction (in dπ–π* synergic bonding, $n = 1$ or 2), which ultimately increases the global concentration of catalytically active L_nPd^0 available for reaction with aryl halide in the first committed step in the general catalytic cycle(s) (oxidative addition). Decreasing electron density on the aryl moiety of the dba-*n*,*n*′-Z ligand stabilizes the Pd^0–η^2-dba interaction, reducing catalytic activity. The specific type of dba-*n*,*n*′-Z ligand appears to also play a stabilizing role in the catalytic cycle, preventing Pd agglomeration, and increasing catalyst longevity. A subtle balance therefore exists between the L_nPd^0 concentration (and the associated catalytic activity) and catalyst longevity. Changing the type of dba-*n*,*n*′-Z ligand controls the concentration of L_nPd^0 and the rate of the oxidative addition step, and not other intimate steps within the catalytic cycle(s), for example, transmetallation (or carbopalladation) and reductive elimination. The role of dba-*n*,*n*′-Z ligands in Heck arylation is more convoluted and dependant on the alkene substrate employed, although trends have emerged. Changes in the structure of dba-*n*,*n*′-Z had a minimal affect on Buchwald–Hartwig aryl amination processes. A secondary Michael reaction of dba-*n*,*n*′-Z with amine and/or base effectively lessens its interference in the catalytic cycle.

Keywords: arylation · C–C coupling · homogeneous catalysis · kinetics · palladium

Introduction

Carbon–carbon and carbon–heteroatom bond-forming processes mediated by Pd^0 are amongst the most important and powerful in synthesis,[1] which has led global interest in the design and development of highly active Pd catalysts/precatalysts[2] for these processes, particularly in Hartwig–Buchwald amination,[3] Heck,[4] Sonogashira,[5] Stille[6] and Suzuki–Miyaura[7] reactions. These studies have traditionally focused on the design and optimisation of σ-donor ligands, which are then added in situ to various Pd^0 and Pd^{II} precursors.[8] A phosphine-free Pd^0 precursor[9] is the air-stable complex $[Pd^0dba_3]$ (dba = *E*,*E*-dibenzylideneacetone),[10] first prepared by Ishii and co-workers.[11] Donor ligands (L) such as phosphines, are routinely added to this precursor to generate complexes of the type "$L_2Pd^0(\eta^2\text{-dba})$". The importance associated with dba dissociation from electron-rich Pd^0 species containing monodentate phosphine ligands, has been systematically investigated by Amatore and Jutand.[12] Cyclic voltametric, chronoamperometry and UV spectro-

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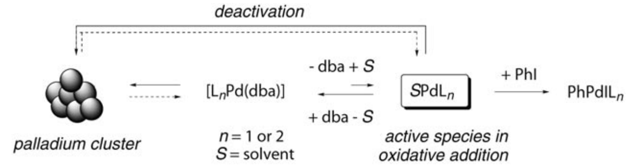
scopic experiments elegantly demonstrate that the most reactive Pd^0 species in the oxidative addition with aryl halides such as iodobenzene, is the lowest ligated complex "L_nPd^0" ($n=1$ or 2).[13] Ligation by dba (a π-acid), which ultimately stabilizes the Pd^0 centre via η^2-alkene coordination,[14] diminishes the concentration of the active catalyst species L_nPd^0 (Scheme 1). As well as lowering the concentration of L_nPd^0, dba (and other π-acids) may reduce Pd^0 agglomeration (to produce clusters/colloids).

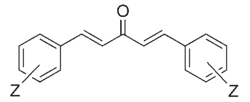


Scheme 1. Ligation of dba to Pd^0 which diminishes the concentration of catalytically active Pd^0.

Crucially, there is an antagonistic effect between the high intrinsic reactivity of the L_nPd^0 complex and its concentration in the equilibrium between L_nPd^0(dba) and L_nPd^0. Indeed, if L is very electron rich, as is the case for trialkylphosphines or N-heterocyclic carbenes, the L_nPd^0(dba) complex will be more stable because the dba may accept the electrons and consequently the equilibrium will be more shifted towards L_nPd^0(dba), thus decreasing the overall reactivity.

One may interpret that dba is a non-spectator ligand in the true sense of the catalytic cycle for cross-coupling reactions. Clearly dba is a spectator ligand in stabilization of L_nPd^0 to give [$L_nPd^0(\eta^2$-dba)], which controls catalyst activity and longevity. However, under certain conditions dba could also be involved in intimate steps within the catalytic cycle. Cationic Pd^{II} complexes ligated by dba have been detected using ESI-MS/MS techniques in intermolecular Heck arylation, providing direct evidence that dba could affect overall rates more so than in other cross-coupling reactions.[15] Other alkenic π-acids, for example, fumaronitrile,[16] *p*-fluorostyrene[17] as well as several other alkenes,[18] are known to play significant roles in cross-coupling reactions, a property that is arguably underutilized.[19] In these reactions it is believed that the accepting alkene ligand binds to and removes electron density from the metal centre (Pd or Ni), thereby facilitating an otherwise difficult reductive elimination step in $C(sp^3)-C(sp^3)$ cross-coupling.

In a recent communication our group has demonstrated that the strength of Pd^0–η^2-dba coordination is affected by the π-electron accepting ability of the dba ligand.[20] Synergic effects (dπ–π* backbonding) appear to control the rate of dissociation of the dba ligand from Pd^0. A series of dinuclear Pd^0 complexes, possessing aryl-substituted dba ligands, generically represented as Pd^0_x(dba-R)$_y$, have previously been prepared by our group.[20,21] The series can be broken down into two distinct classes, [Pd^0_2(dba-*n,n′*-Z)$_3$] and [Pd^0(dba-*n,n′*-Z)$_2$], and although a third class is presented as [Pd^0_2(dba-*n,n′*-Z)$_2$], there is only one complex that possesses this unusual ligand/Pd ratio (*n,n′*-Z = 3,3′-NO_2), see Figure 1; the parent dba ligand will now be referred to as dba-4,4′-H to avoid confusion. In Suzuki–Miyaura cross-coupling it was determined that electron-withdrawing substituents such as NO_2 or CF_3, deactivate the active catalyst species (L_nPd^0), whereas strongly donating substituents such as OMe, increase catalytic activity over that of the dba-4,4′-H ligand. In collaboration with the group of Jutand, we have established that the dba-*n,n′*-Z ligand principally influences the oxidative addition reaction with aryl iodides.[22] Indeed, considering PPh_3 as ligand, the overall rate of the oxidative addition was faster when Z was an electron-donating group, primarily because the greater electron-donating capacity of the Z group, the lower the affinity of dba-4,4′-Z for $Pd^0(PPh_3)_2$ is, which leads to higher concentrations of $Pd^0(PPh_3)_2$. This effect will be more dominant when the oxidative addition step is rate-limiting, as is the case when aryl chlorides are used as coupling partners. The work also built on the insightful studies conducted by Scrivanti and coworkers who demonstrated that the π-accepting ability of an alkene in (P,N)$Pd^0(\eta^2$-alkene) complexes determines its catalytic reactivity and overall stability.[23]



Z = H (dba), 4,4′-OMe, 4,4′-*t*Bu, 3,5,3′,5′-OMe, 3,3′-NO_2, 4,4′-CF_3, 4,4′-F, 4,4′-Cl, 4,4′-Br

[Pd(dba-*n,n′*-Z)$_2$]
- [Pd(dba)$_2$]
- [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)$_3$]
- [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)$_3$

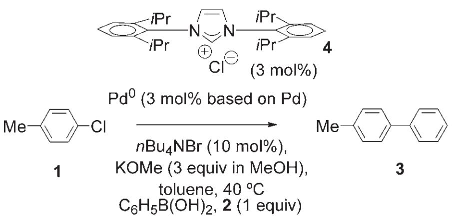
[Pd_2(dba-*n,n′*-Z)$_2$]
- [Pd_2(dba-3,3′-NO_2)$_2$]

Figure 1. Various binuclear [Pd_x(dba-R)$_y$] complexes ($x=1$ or 2; $y=2$ or 3).

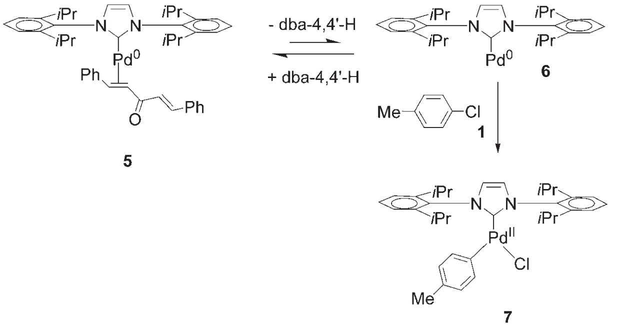
In this study, we present evidence that the "dba effect" is generic in several common palladium(0)-mediated processes. The catalytic activity of all the Pd^0 complexes as primary sources of Pd^0 in combination with donor ligands (N-heterocyclic carbenes or phosphines) has been assessed in Suzuki–Miyaura cross-coupling, α-arylation of esters, intermolecular Heck arylation and Buchwald–Hartwig amination. The affect of the aryl substituent in dba-*n,n′*-Z on the reaction rate and enantioselectivity is further assessed in an asymmetric variant of the intermolecular Heck arylation.

Results and Discussion

Suzuki–Miyaura cross-coupling—The effect of donor ligand: The pure Pd^0-precursor complexes were evaluated against a highly active catalyst system recently reported by Caddick and co-workers for Suzuki–Miyaura coupling.[24] We selected the reaction of 4-chlorotoluene (**1**) with phenylboronic acid (**2**) catalyzed by [Pd^0_2(dba-4,4′-H)$_3$] (3 mol %)/NHC ligand (derived from imidazolium salt **4**) (3 mol %) to give **3** (Scheme 2). Based on the ligand/Pd ratio, the generation of a mono-NHC ligand Pd^0 species **5** was expected, which would be stabilized by ligation with dba-4,4′-H (Scheme 3). The initial oxidative addition with **1** was thus expected to involve dissociation of the dba ligand from **5** to generate **6** (which is likely to be solvated), which finally gives Pd^{II}-intermediate **7**.



Scheme 2. Benchmark reaction for assessing the effect of aryl substitution in Pd^0 precursor complexes containing dba-*n*,*n*′-Z ligands.



Scheme 3. Synthesis of complex **7**.

The reaction was used as a benchmark for all of the Pd^0-precursor complexes. Each reaction was monitored by high-resolution gas chromatography (HRGC) analysis, allowing the kinetics to be determined (pseudo first-order rates for consumption of **1**) (Table 1).

Table 1. Pseudo first-order rates for consumption of **1** in Suzuki–Miyaura cross-coupling for different Pd^0 precursor complexes.[25]

Entry	Pd^0 Precursor	Rate/s^{-1}
	[Pd^0(dba-*n*,*n*′-Z)$_2$]	
1	4,4′-H	3.11×10^{-5} ($\pm2.3\times10^{-6}$)
2	4,4′-CF_3	2.25×10^{-5} ($\pm3.6\times10^{-6}$)
3	3,3′,5,5′-OMe	6.19×10^{-5} ($\pm6.9\times10^{-6}$)
	Pd^0_2(dba-*n*,*n*′-Z)$_3$	
4	4,4′-H	3.69×10^{-5} ($\pm2.5\times10^{-6}$)
5	4,4′-CF_3	2.85×10^{-5} ($\pm2.1\times10^{-6}$)
6	4,4′-F	3.49×10^{-5} ($\pm3.3\times10^{-6}$)
7	4,4′-*t*Bu	3.83×10^{-5} ($\pm3.0\times10^{-6}$)
8	4,4′-OMe	5.47×10^{-5} ($\pm5.1\times10^{-6}$)
	[Pd^0_2(dba-*n*,*n*′-Z)$_2$]	
9	3-NO_2	6.24×10^{-6} ($\pm9.6\times10^{-7}$)

The rate for the reaction depicted in Scheme 2 using [Pd^0(dba-4,4′-H)$_2$] as the Pd^0 precursor was $3.11\times10^{-5}\,s^{-1}$ ($\pm2.3\times10^{-6}$) (entry 1). As expected, there is a small difference in catalytic activity for the different dba-4,4′-H/Pd ratios (entries 1 and 4); increasing dba-4,4′-H concentration should decrease catalytic activity. The electron-withdrawing trifluoromethyl group reduces the rate in both [Pd^0(dba-4,4′-CF_3)$_2$] and [Pd^0_2(dba-4,4′-CF_3)$_3$] complexes (entries 2 and 5). On the other hand, [Pd^0(dba-3,3′,5,5′-OMe)$_2$] (entry 3) significantly increases the rate of reaction relative to [Pd^0(dba-4,4′-H)$_2$]. The electron-withdrawing fluoro substituent in [Pd^0_2(dba-4,4′-F)$_3$] exhibits a similar rate as for [Pd^0_2(dba-4,4′-H)$_3$] (compare entries 4 and 6). The *tert*-butyl substituent (entry 7) showed a slightly higher rate, however, the error hinders a direct comparison with [Pd^0_2(dba-4,4′-H)$_3$]. The electron-donating 4-methoxy substituent did give a substantially higher rate (entry 8). The Pd^0 precursor complex exhibiting the slowest rate was [Pd^0_2(dba-3,3′-NO_2)$_2$] (entry 9).[26] This is by some margin the most π-accepting ligand of the series of dba-*n*,*n*′-Z ligands evaluated.

In these experiments the rates are affected by the nature of the substituent in the dba-*n*,*n*′-Z ligand. These observed effects are substrate independent.[20] A Hammett plot, utilising σ_{para} values, illustrates that the substituent effect is non-linear (Figure 2a). A linear relationship was established for the effect of the substituent in dba-*n*,*n*′-Z ligands in the stoi-

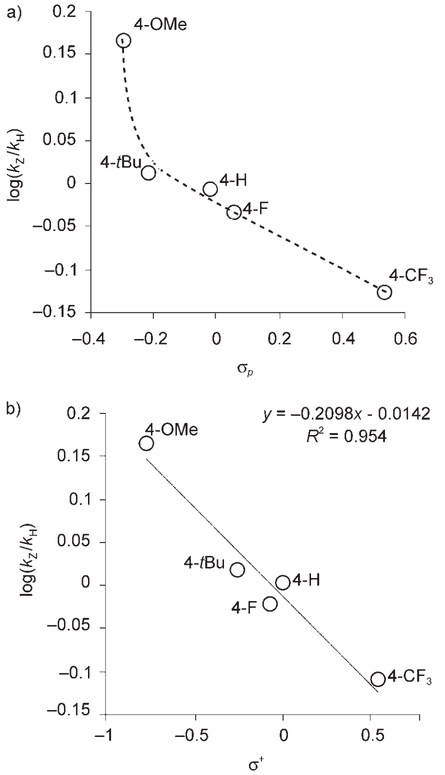
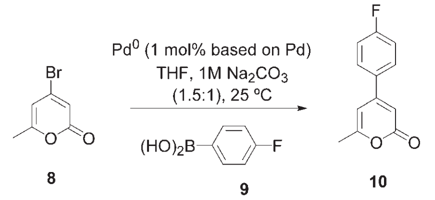


Figure 2. a) Hammett plot (using σ_{para} values) for the reaction depicted in Scheme 1 mediated by [Pd^0_2(dba-4,4′-Z)$_3$] complexes (Z = OMe, *t*Bu, H, F or CF_3); b) Hammett plot using σ^+ values.

chiometric oxidative addition reaction of PhI (2 mM) with the [Pd^0(PPh$_3$)$_2$] complex generated from [Pd$^0_2$(dba-4,4′-Z)$_3$] (1 mM) and PPh$_3$ (4 mM) in DMF at 20 °C ($\rho = -1.7$).[22]

We have not included [Pd$^0_2$(dba-3,3′-NO$_2$)$_2$] for comparison as this possesses one less dba-4,4′-Z ligand than the [Pd$^0_2$(dba-*n*,*n*′-Z)$_3$] complexes. However, we can state that the 3-NO$_2$ group ($\log(k_{3\text{-NO}_2}/k_\text{H}) = -0.772$; $\sigma_\text{m} = 0.71$) would lie significantly away from the curve (Figure 2). This indicates that there could be a change in the rate determining step as a function of the different substituents (from oxidative addition to dba-3,3′-NO$_2$ dissociation from Pd^0). A Hammett plot, utilizing the σ^+ values,[27] which takes into account resonance stabilisation, exhibits a less pronounced non-linear trend (Figure 2b), which indicates a direct correlation of the *para*-substituent of dba-*n*,*n*′-Z with rate. The 3-NO$_2$ substituent (not depicted) lies away from the curve when the σ^+ and σ_p values are compared with $log(k_{3\text{-NO}_2}/k_\text{H})$.

Suzuki–Miyaura cross-coupling—In a ligand-free catalyst system: The Pd^0 complexes were next evaluated in a ligand-free system[28] for the cross-coupling of the activated bromo-2-pyrone (**8**) with 4-fluorophenylboronic acid (**9**) to give **10** (Scheme 4).[29] Given the absence of an activating donor ligand (e.g. NHC or PR$_3$ ligand) it was predicted that the dba-4,4′-Z ligand could act as a donor and/or acceptor. The rates for the pseudo first order consumption of **8** are listed in Table 2 (established by HRGC analysis).

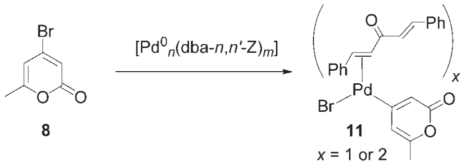


Scheme 4. Benchmark reaction for a ligand-free type system.

These data indicate that the choice of the substituent on the dba ligand influences the so-called ligand-free system, particularly for [Pd^0(dba-*n*,*n*′-Z)$_2$] complexes (entries 1–3). Initial ligand dissociation from the [Pd^0_x(dba-*n*,*n*′-Z)$_y$] complexes ($x = 1$ or 2; $y = 2$ or 3) is assumed to be facile, given the well-known solution behaviour of [Pd$_2$(dba-4,4-H)$_3$] and related complexes,[30] therefore oxidative addition of **8** with Pd^0 to give **11** should also be promoted by the donating properties of the dba-*n*,*n*′-Z ligands (Scheme 5).

Table 2. Pseudo first-order rates for the consumption of **8** in Suzuki–Miyaura cross-coupling for different Pd^0 precursor complexes.

Entry	Pd^0 Precursor	Rate/s^{-1}
		[Pd^0(dba-*n*,*n*′-Z)$_2$]
1	4,4′-H	3.63×10^{-4} ($\pm5.6\times10^{-5}$)
2	4,4′-CF$_3$	2.87×10^{-4} ($\pm3.2\times10^{-5}$)
3	3,3′,5,5′-OMe	6.34×10^{-4} ($\pm1.6\times10^{-5}$)
		[Pd$^0_2$(dba-*n*,*n*′-Z)$_3$]
4	4,4′-H	6.00×10^{-4} ($\pm4.1\times10^{-5}$)
5	4,4′-F	6.24×10^{-4} ($\pm1.5\times10^{-5}$)
6	4,4′-*t*Bu	6.20×10^{-4} ($\pm1.2\times10^{-5}$)
7	4,4′-OMe	5.29×10^{-4} ($\pm6.6\times10^{-5}$)
		[Pd$^0_2$(dba-*n*,*n*′-Z)$_2$]
8	3-NO$_2$	5.75×10^{-5} ($\pm7.5\times10^{-6}$)



Scheme 5.

Running the reactions at higher concentrations (0.33 M rather than 0.164 M with respect to **8**) results in the precipitation of Pd black. The π-accepting properties of the dba-*n*,*n*′-Z ligand must also play a vital role in these reactions, although there appears to be a very fine balance. The difference in reactivity seen between [Pd$^0_2$(dba-4,4′-F)$_3$] and [Pd$^0_2$(dba-4,4′-OMe)$_3$] (entries 5 and 7) does not fit so readily into the overall model, as the latter complex would be expected to be more reactive.

The significant difference in rate between [Pd^0(dba-4,4′-H)$_2$] and [Pd$^0_2$(dba-4,4′-H)$_3$] (entries 1 and 4), and lesser differences seen for [Pd$^0_2$(dba-*n*,*n*′-Z)$_3$]-type complexes (entries 4–7), suggests that in the ligand-free system the global concentration of dba-*n*,*n*′-Z ligand is a more dominant factor than subtle modifications to the dba-*n*,*n*′-Z ligand structure. This was confirmed by increasing the dba-4,4′-H concentration in reactions mediated by [Pd$^0_2$(dba-4,4′-H)$_3$]; the reaction profiles are shown in Figure 3. Higher concentrations of dba-4,4′-H have a dramatic affect on the rates. In the presence of 2 mol% dba-4,4′-H, the rate is 3.65×10^{-4} s^{-1} ($\pm7.2\times10^{-5)}$. The rate is reduced more so in the presence of 5 mol% dba-4,4′-H (2.63×10^{-4} s^{-1}, $\pm2.8\times10^{-5}$).

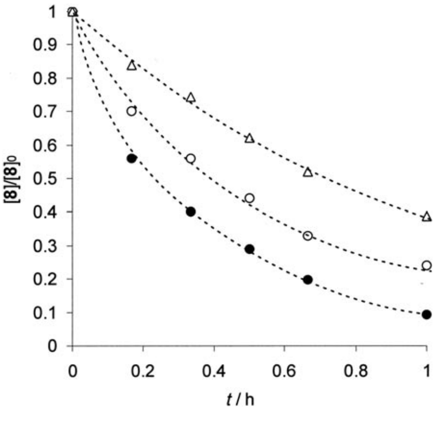
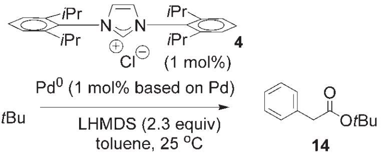


Figure 3. Increasing dba-4,4′-H concentration in the Suzuki–Miyaura reaction of **8** and **9** to give **10** mediated by [Pd$^0_2$(dba-4,4′-H)$_3$] (dashed lines serve as a guide to the eye). ●: [Pd$^0_2$(dba-4,4′-H)$_3$]; ○: [Pd$^0_2$(dba-4,4′-H)$_3$] + 2 mol% dba (based on Pd^0); △: [Pd$^0_2$(dba-4,4′-H)$_3$] + 5 mol% dba (based on Pd^0).

So, although higher dba concentration is expected to hinder Pd agglomeration (catalyst decomposition), it does so at the expense of catalyst activity, blocking required coordination sites on Pd^0.

α-Arylation of esters: The α-arylation of ester compounds has emerged as a potentially useful tool for drug discovery, amongst other applications.[31] The benchmark α-arylation reaction employed to evaluate the Pd^0 precursor complexes was that concerning cross-coupling of bromobenzene (**12**) and *tert*-butyl acetate (**13**), using LHMDS as the base, to give the α-arylated product **14** (Scheme 6).



Scheme 6. Benchmark α-arylation reaction.

The reaction is mediated by a 1:1 mixture of $[Pd^0(dba\text{-}4,4'\text{-}H)_2]$ and an NHC ligand (generated in situ from the imidazolium salt **4**), reported by Hartwig and co-workers to proceed in 87% isolated yield after 12 h.[32] With this information to hand, the reaction profiles and pseudo first-order rates for the consumption of **12** were determined for $[Pd^0_2(dba\text{-}n,n'\text{-}Z)_3]$ (Z=H, F, CF_3, *t*Bu and OMe) and $[Pd^0_2(dba\text{-}3,3'\text{-}NO_2)_2]$ complexes (Figure 4 and Table 3).

Changing substituents in the dba-*n*,*n*′-Z ligands again affects the rates. The catalyst precursors $[Pd^0_2(dba\text{-}4,4'\text{-}CF_3)_3]$ and $[Pd^0_2(dba\text{-}3,3'\text{-}NO_2)_2]$, containing electron-withdrawing ligands, both exhibit induction periods, which is intriguing. At about 4–5 h, both reactions begin to turnover. The origin of the induction period is unclear. It is tentatively proposed that the reaction of the NHC ligands with $[Pd^0_2(dba\text{-}4,4'\text{-}CF_3)_3]$ and $[Pd^0_2(dba\text{-}3,3'\text{-}NO_2)_2]$, respectively, is much slower relative to $[Pd^0_2(dba\text{-}4,4'\text{-}H)_3]$. Alternatively, there is the possibility that the dba-*n*,*n*′-Z ligand is being consumed (where Z is CF_3 or NO_2), governed by a slow secondary rate which will be affected by the nature of Z; reaction of the ester enolates, or aryl halide, with the dba-*n*,*n*′-Z ligands has not been found in these α-arylation reactions (by HRGC/MS), nor have any derived products been isolated by column chromatography.

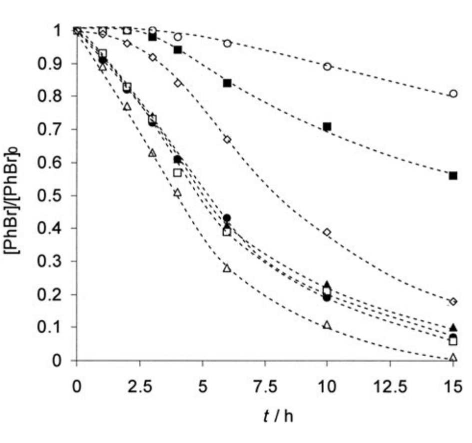
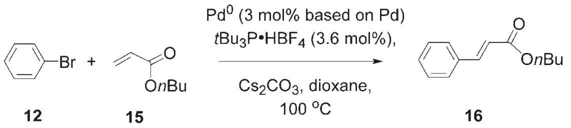


Figure 4. Reaction profiles from the reaction depicted in Scheme 6 (dashed lines serve as a guide to the eye). ○: $[Pd^0_2(dba\text{-}3,3'\text{-}NO_2)_2]$; ■: $[Pd^0_2(dba\text{-}4,4'\text{-}CF_3)_3]$; ◇: $[Pd^0_2(dba\text{-}4,4'\text{-}F)_3]$; ▲: $[Pd^0_2(dba\text{-}4,4'\text{-}H)_3]$; □: $[Pd^0_2(dba\text{-}4,4'\text{-}tBu)_3]$; ●: $[Pd^0_2(dba\text{-}4,4'\text{-}OMe)_3]$; △: $[Pd^0_2(dba\text{-}3,3',5,5'\text{-}OMe)_3]$.

Table 3. Pseudo first-order rates for the consumption of **12** in α-arylation of **13** for different Pd^0-precursor complexes.

Entry	Pd^0 Precursor (Z)	Rate/s^{-1}
		$[Pd^0_2(dba\text{-}n,n'\text{-}Z)_3]$
1	4,4′-H	4.57×10^{-5} ($\pm3.8\times10^{-6}$)
2	4,4′-CF_3	1.29×10^{-5} ($\pm7.9\times10^{-7}$)
3	3,3′,5,5′-OMe	9.37×10^{-5} ($\pm2.8\times10^{-6}$)
4	4,4′-F	3.80×10^{-5} ($\pm4.8\times10^{-6}$)
5	4,4′-*t*Bu	4.99×10^{-5} ($\pm4.5\times10^{-6}$)
6	4,4′-OMe	5.44×10^{-5} ($\pm2.8\times10^{-6}$)
		$[Pd^0_2(dba\text{-}n,n'\text{-}Z)_2]$
7	3-NO_2	4.86×10^{-6} ($\pm6.1\times10^{-7}$)

Intermolecular Heck arylation: The Pd^0 complexes were next assessed in Heck arylation, using similar reaction conditions to those reported by Fu and co-workers (Scheme 7).[33]



Scheme 7. Benchmark Heck arylation of *n*-butyl acrylate **15** mediated by a Pd/$tBu_3P\cdot HBF_4$ catalyst system.

Note that we employed the air-stable salt, $tBu_3P\cdot HBF_4$ instead of the free ligand, tBu_3P. The kinetic profiles for the reaction of **12** with *n*-butyl acrylate (**15**) are shown in Figure 5; the rates are given in Table 4.

The kinetic profiles from the reaction of **12** with **15** to give **16** exhibits broad rate differences for the Pd^0-precursor complexes investigated. An induction period is seen for $[Pd^0_2(dba\text{-}3,3'\text{-}NO_2)_2]$, whereas induction periods for other Pd^0 precursor complexes were less pronounced. Curiously, the $[Pd^0_2(dba\text{-}4,4'\text{-}tBu)_3]$ complex is more deactivated, relative to $[Pd^0_2(dba\text{-}4,4'\text{-}H)_3,]$, in this reaction. The other complexes fall into the same reactivity sequence mentioned above. To give an idea of the difference in reactivity of all the $Pd^0_x(dba\text{-}R)_y$ complexes, an identical reaction was conducted using $Pd(OAc)_2$ (3 mol%). A rate of 6.82×10^{-5} s^{-1} ($\pm9.7\times10^{-6}$) was determined. Although $Pd(OAc)_2$ does not always out perform $Pd^0_x(dba\text{-}H)_y$ complexes (agglomeration is sometimes seen with $Pd(OAc)_2$, particularly under ligand-free conditions),[28,37] this example clearly shows that the rate is substantially faster using a $Pd(OAc)_2$ precatalyst.

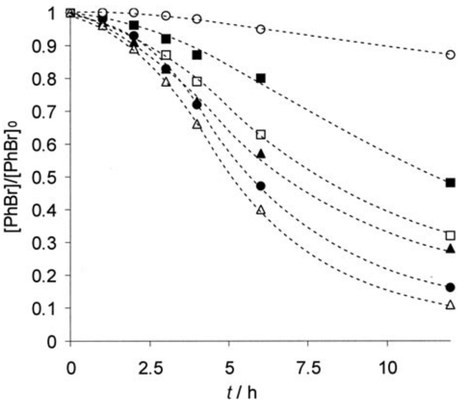


Figure 5. Reaction profiles from the reaction depicted in Scheme 7 (dashed lines serve as a guide to the eye). ○: [Pd^0_2(dba-3,3′-NO_2)$_2$]; ■: [Pd^0_2(dba-4,4′-CF_3)$_3$]; ▲: [Pd^0_2(dba-4,4′-H)$_3$]; □: [Pd^0_2(dba-4,4′-*t*Bu)$_3$]; ●: [Pd^0_2(dba-4,4′-OMe)$_3$]; △: [Pd^0_2(dba-3,3′,5,5′-OMe)$_3$].

Table 4. Pseudo first-order rates for the consumption of **12** in Heck arylation for different Pd^0 precursor complexes.

Entry	Pd^0 Precursor (Z)	Rate/s^{-1}
	[Pd^0_2(dba-*n*,*n*′-Z)$_3$]	
1	4,4′-H	3.34×10^{-5} ($\pm1.3\times10^{-6}$)
2	4,4′-CF_3	2.04×10^{-5} ($\pm7.6\times10^{-6}$)
3	3,3′,5,5′-OMe	6.13×10^{-5} ($\pm5.3\times10^{-6}$)
4	4,4′-*t*Bu	3.11×10^{-5} ($\pm1.4\times10^{-6}$)
5	4,4′-OMe	5.13×10^{-5} ($\pm5.1\times10^{-6}$)
	[Pd^0_2(dba-*n*,*n*′-Z)$_2$]	
6	3-NO_2	4.12×10^{-6} ($\pm6.2\times10^{-7}$)

To test the substrate dependence in Heck arylation using the [Pd^0_2(dba-3,3′,5,5′-OMe)$_3$] and [Pd^0_2(dba-4,4′-CF)$_3$] Pd^0-precursor complexes, relative to [Pd^0_2(dba-4,4′-H)$_3$], a series of reactions were carried out in parallel using the ASW 2000 from ChemSpeed technology (Figure 6). In the first set of reactions (I–III), using **15** as the alkene substrate, it is apparent that the dba-4,4′-Z ligands play a role in the majority of examples, regardless of the structure of the aryl halide. [Pd^0_2(dba-3,3′,5,5′-OMe)$_3$] gives the highest conversions, whereas [Pd^0_2(dba-4,4′-CF)$_3$] gives the lowest. In reaction IV, that of *p*-fluorobromobenzene with **15**, indicates that [Pd^0_2(dba-4,4′-H)$_3$] is the most active precursor complex. For reactions employing styrene as a substrate (reactions V–IX), the reactivity sequence is as expected. However, the differences between [Pd^0_2(dba-4,4′-H)$_3$] and [Pd^0_2(dba-3,3′,5,5′-OMe)$_3$] is relatively small, albeit still in favour of the latter. The [Pd^0_2(dba-4,4′-CF)$_3$] complex is on the other hand notably less active.

In this series, the results indicate that styrene, in excess relative to dba-*n*,*n*′-Z, effectively competes with dba-*n*,*n*′-Z ligation to Pd^0, thus playing a more dominant role in the catalytic cycle than the more sterically hindered alkene **15**. It has been demonstrated by Jutand and Amatore that whenever the oxidative addition is not rate-determining, the decelerating effect of the alkene on this reaction is in favour of a higher efficiency in the catalytic cycle.[34] Effectively, alkene coordination reduces the global concentration of "L_nPd^0", bringing the rate of the oxidative addition closer to that of the carbopalladation step, that is, alkene nucleophilic attack on the Pd^{II}(aryl)halide complex formed in the oxidative addition step, which is usually the rate determining step.[35] A mechanism is outlined in Scheme 8 which shows the roles of the alkene ligands in the catalytic cycle (the alkenyl product may also play a role).

The reactive Pd^0-species **I** is assumed to be monoligated[13a] by *t*Bu_3P (solvated by dioxane), the concentration of this species will be diminished by both the dba-*n*,*n*′-Z ligand and the alkene reactant (styrene or *n*-butyl acrylate), to give **II** and **III**, respectively. The concentration of **II** and **III** will be determined by the strength of the Pd^0–η^2-alkene interaction. Crucially, for monoligated species **III** direct oxidative addition gives complex **VII**, which can either undergo carbopalladation to give **V** or alkene ligand loss to give **IV**. The relative conversions seen in Figure 6, for styrene in particular, indicate that there is a delicate and subtle balance be-

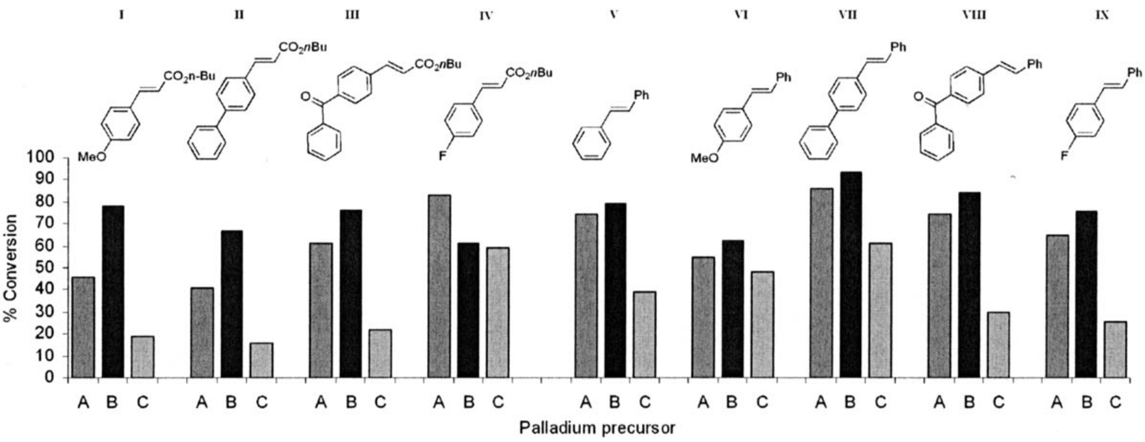
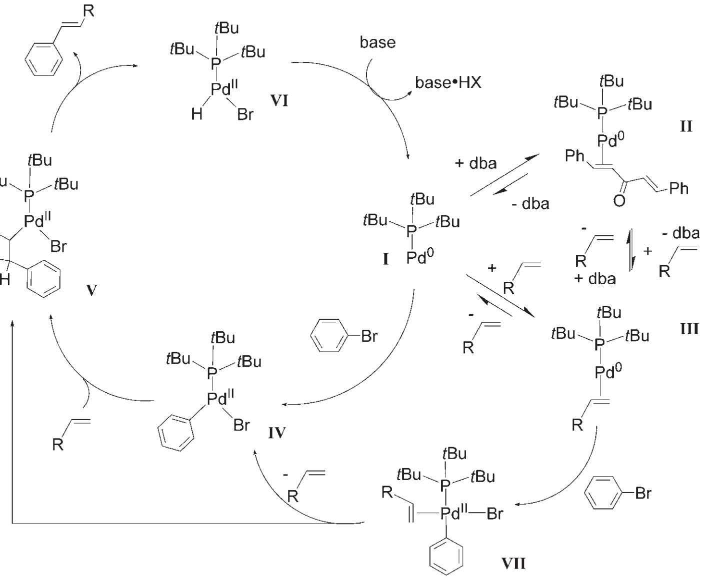
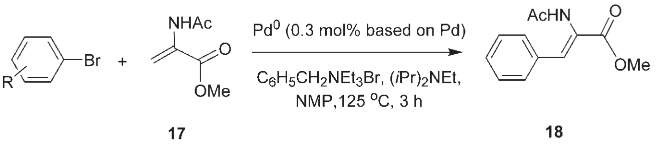


Figure 6. Heck arylation mediated by A = [Pd^0_2(dba-4,4′-H)$_3$]; B = [Pd^0_2(dba-3,3′,5,5′-OMe)$_3$]; C = [Pd^0_2(dba-4,4′-CF)$_3$]. Reagents and conditions, see Scheme 7: *t*$Bu_3P\cdot HBF_4$ (6 mol%) was used in the reactions employing styrene. Conversions were determined by HRGC/MS and calculated against an internal standard (dihexyl ether); yield calculations include corrected response factors for reagents and products.



Scheme 8. Roles for alkene ligands in Heck arylation. Note: We expect that all 14-electron intermediates will be stabilized by solvent (as more stable 16-electron complexes); in equilibrium with dimeric Pd species or stabilized by suitable agostic interactions.[36]



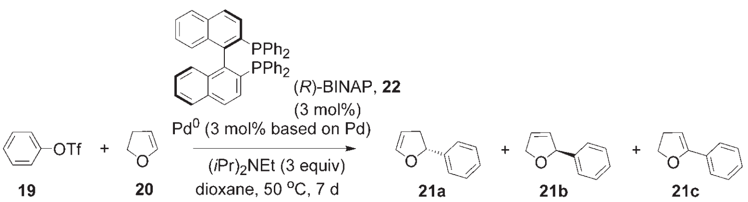
Scheme 9. Heck arylation of methyl 2-acetamidoacrylate.

tween the equilibria of **I** and **II** and **I** and **III**; presumably **II** and **III** are also in equilibrium. It can thus be proposed that **III** is favoured when R = Ph and the dibenzylideneacetone ligand is dba-3,3′,5,5′-OMe or dba-4,4′-H.

We also evaluated $[\mathrm{Pd}^0_2(\text{dba-4,4}'\text{-H})_3]$, $[\mathrm{Pd}^0_2(\text{dba-3,3}',5,5'\text{-OMe})_3]$ and $[\mathrm{Pd}^0_2(\text{dba-4,4}'\text{-CF})_3]$ in intermolecular Heck arylation of methyl 2-acetamidoacrylate with 4-bromobiphenyl and 4-fluoro-bromobenzene (reactions I and II, respectively, Figure 7), using a protocol developed by de Vries and co-workers (Scheme 9).[37]

The results exhibit a trend which is similar to the reactions conducted in the presence of styrene, indicating that methyl 2-acetamidoacrylate also plays a role in the catalytic cycle (other than in carbopalladation).

Effects on the asymmetric intermolecular Heck arylation: Having established the effects of the various dba-*n*,*n′*-Z ligands in intermolecular Heck arylation, we speculated that the regio- and enantioselectivity could be affected in an asymmetric variant, particularly if the dba-*n*,*n′*-Z ligand is bound to the $\mathrm{Pd}^{\mathrm{II}}$ intermediate undergoing carbopalladation—the carbon–carbon bond forming step in the catalytic cycle where the chiral centre is generated. The protocol selected was one initially reported by Hayashi and co-workers,[38] but developed by Keay and co-workers.[39] The reaction of phenyltriflate (1 equiv) with 2,3-dihydrofuran (6 equiv), promoted by a $[\mathrm{Pd}^0_2(\text{dba-4,4}'\text{-H})_3]$ (3 mol % Pd^0)/(*R*)-BINAP[40] (3 mol %) catalyst system in the presence of DIPEA (3 equiv) in dioxane at 50 °C for 7 d, was used as a benchmark (Scheme 10). The major product is (*R*)-**21a**. Minor products were expected, for example, (*S*)-**21b** and **21c**. We were able to reproduce the results[39] reported for $[\mathrm{Pd}^0_2(\text{dba-4,4}'\text{-H})_3]$ (entry 1, Table 5). For $[\mathrm{Pd}^0_2(\text{dba-4,4}'\text{-}$



Scheme 10. Benchmark reaction for asymmetric Heck arylation.

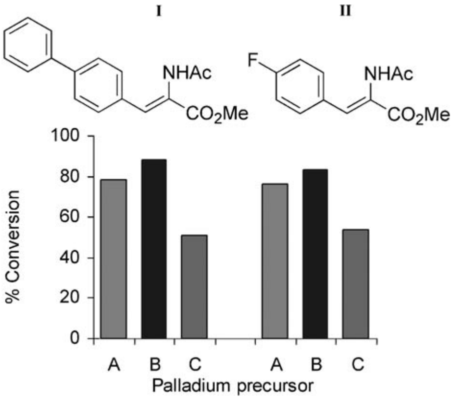


Figure 7. Heck alkenylation reactions mediated by A = $[\mathrm{Pd}^0_2(\text{dba-4,4}'\text{-H})_3]$; B = $[\mathrm{Pd}^0_2(\text{dba-3,3}',5,5'\text{-OMe})_3]$; C = $[\mathrm{Pd}^0_2(\text{dba-4,4}'\text{-CF})_3]$. Reagents and conditions, see Scheme 7: aryl bromide (1 equiv), **17** (1.1 equiv), (*i*Pr)$_2$NEt (1.15 equiv), $C_6H_5CH_2NEt_3Br$ (4.6 equiv), Pd^0 (0.30 mol % with respect to aryl bromide), NMP, at 125 °C, 3 h.

Table 5. Application of various Pd^0 precursor complexes in the Heck arylation of 2,3-dihydrofuran **20**.[a]

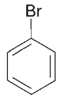
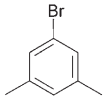
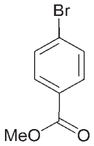
Entry	Pd^0 Precursor (Z)	Yield/ %	*ee*/% (*R*)-**23a**[b]	*ee*/% (*S*)-**23b**[b]	Selectivity for **23a**/%[c]
			$[\mathrm{Pd}^0_2(\text{dba-}n,n'\text{-Z})_3]$		
1	4,4′-H[d]	51	63	21	95
2	4,4′-CF_3	42	61	18	93
3	3,3′,5,5′-OMe	63	65	22	94
4	4,4′-F	69	68	41	95
5	4,4′-OMe	63	62	20	94

[a] Yields and the enantiomeric excess (*ee*) values represent an average from at least two separate runs. Yields given are after column chromatography. [b] The enantiomeric excess was determined on a β-cyclodextrin chiral column by HRGC. The ee values and product regioisomeric selectivities were determined by analysis of the crude reaction products by HRGC. [c] In all cases < 1 % of **21c** was detected by HRGC. [d] The reported conversion[39] to products is 56 %: (*R*)-**21a** (52 % yield, 66 % *ee*); (*S*)-**21b** (2 % yield; 15 % *ee*); **21c** (1 % yield).

CF)$_3$] catalytic activity was reduced, whereas the enantioselectivity and product selectivity were near identical to [Pd$^0_2$(dba-4,4′-H)$_3$] (entry 2, Table 5).

For [Pd$^0_2$(dba-3,3′,5,5′-OMe)$_3$], [Pd$^0_2$(dba-4,4′-F)$_3$] and [Pd$^0_2$(dba-4,4′-OMe)$_3$] the conversions improved to 63, 69 and 63 %, respectively (entries 3–5, Table 5). The minor differences in enantiomeric excess observed for (*R*)-**21a** provide indirect evidence that the dba-*n*,*n*′-Z ligands are not involved in the carbopalladation step of the catalytic cycle. The higher enantiomeric excess of (*S*)-**21b** (41 %), relative to the other Pd^0-precursor complexes, is worthy of note. The highest enantiomeric excess recorded for (*R*)-**21a** was with [Pd$^0_2$(dba-4,4′-F)$_3$], and of the series, exhibits the most marked affect on the stereochemical outcome. The higher yield observed in the presence of dba-4,4′-F suggests that this ligand plays a greater stabilizing role, preventing the agglomeration/precipitation of Pd from the reaction over the long reaction time (7 d); the balance between catalyst activity and stability being the key to higher yields in this particular process.

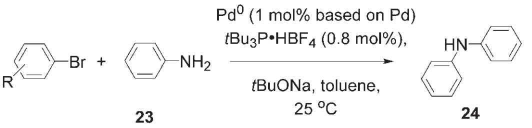
Table 6. Application of various Pd^0 precursor complexes in Buchwald–Hartwig aryl amination reactions.[a]

Entry	Aryl bromide	Pd/mol %[b]	*t*/min	Yield/%[c]		
				[Pd^0(dba-*n*,*n*′-Z)$_2$]		
				4,4′-H	3,3′,5,5′-OMe	4,4′-CF$_3$
1		1	10	>99	>99	>99
		0.5	10	>99	>99	>99
		0.2	10	10	27	22
2		1	60	82	72	76
		0.5	60	13	14	9
3		1	60	94	97	98

[a] Reagents and conditions, see Scheme 11. [b] The Pd/L ratio was maintained at 1:0.8 on lowering the overall Pd^0 concentration. [c] This is the yield after column chromatography (purity > 97 %).

Buchwald–Hartwig amination: The Pd^0-catalysed amination of aryl halides has emerged as an important method for the synthesis of aryl amines.[41] It was anticipated that the involvement of dba-*n*,*n*′-Z ligands in the reaction of an aryl halide with amine could be more complex than the other processes. Amines, specifically anilines, are known to react with dba-4,4′-H and related compounds through a Michael addition reaction,[42] which inadvertently would reduce the interference of dba-4,4′-H in the catalytic process. Clearly, a combination of amine and base would serve as a better nucleophile to dba-4,4′-H than any individual reactions of amine or base.[43] We selected the reaction conditions reported by Hartwig's group, employing the monophosphine ligand,[44] *t*Bu$_3$P (Scheme 11).[45]

On a general note, these reactions are more difficult to conduct without the use of a dry-box (in our hands, strict Schlenk techniques were essential and the results were sometimes variable). However, through use of *t*Bu$_3$P·HBF$_4$[46] and pre-mixing the Pd^0 precursor in the presence of the base (*t*BuONa), we were able to effectively carry out the reactions under standard Schlenk techniques. In the first reaction, reaction of PhBr (**12**) with aniline using 1 mol % [Pd^0(dba-4,4′-H)$_2$] and 0.8 mol % *t*Bu$_3$P·HBF$_4$ we able to attain a quantitative yield of **24** in 10 min (entry 1, Table 6). To discern any differences between the Pd^0-precursor complexes, the concentration of [Pd^0(dba-4,4′-H)$_2$] was lowered to 0.5 and 0.2 mol % (the Pd/L ratio was maintained at 1:0.8). The yield dropped substantially going from 0.5 to 0.2 mol %, and some minor differences between [Pd^0(dba-4,4′-H)$_2$], [Pd^0(dba-3,3′,5,5′-OMe)$_2$] and [Pd^0(dba-4,4′-CF$_3$)$_2$] were recorded at 0.2 mol % Pd^0. The reaction of 1-bromo-3,5-dimethylbenzene required 1 mol % Pd^0 for high yield (entry 2). At both 1 mol % and 0.5 mol % Pd^0, negligible differences were seen between the Pd^0-precursor complexes. For the more activated substrate, methyl 4-bromobenzoate, the yields of the products were near identical. These results strongly suggest that the dba-*n*,*n*′-Z ligand plays an insignificant role under the conditions described by Hartwig's group. The isolation of small quantities of mono- and bisaminated products of dba-4,4′-Z suggests that it is consumed under the reaction conditions, although it should be noted that on several occasions unreacted dba-4,4′-Z ligand has also been recovered after careful column chromatography. Overall, it appears that dba-*n*,*n*′-Z ligands play a more innocent role in aryl amination processes.



Scheme 11. Benchmark aryl amination reaction.

Conclusion

In this study we have developed a tuneable concept through modulation of the electronic properties of the non-innocent dibenzylideneacetone (dba) ligands and shown that this significantly affects catalytic activity in several Pd^0-mediated processes. Simple modifications to the ancillary dba-Z ligands surrounding the active Pd^0 species causes dramatic changes in catalytic performance.[47] With the exception of the aryl amination processes, all other reactions investigated indicate that more electron rich dba-*n*,*n*′-Z ligands cause an increase in catalyst activity. Electron deficient dba-*n*,*n*′-Z ligands reduce the rates of reaction in the majority of cases, the exception being in asymmetric Heck arylation, where [Pd$^0{}_2$(dba-4,4′-F)$_3$] gave the highest conversions and enantioselectivities. The 4-fluoro substituent can play two roles electronically: the first effect would be deactivating based on inductive arguments, and the second effect would be activating via mesomeric effects (as a strong π-donor). Given the long reaction times for these reactions (7 d), the dba-4,4′-F ligand will be expected to play a stabilizing role in keeping Pd^0 available for further reaction (avoiding agglomeration/precipitation). The extent of the substituent effect is subtly dependent on individual reaction systems. For the [Pd$^0{}_2$(dba-3,3′,5,5′-OMe)$_3$] complex, the subtle blend of donating substituents which possess electron removal ability (the substituents being in the *meta*-position) appears to find the right balance between catalytic activity and stability. Generally, when electron-donating ligands are employed in Suzuki–Miyaura coupling, α-arylation and Heck arylation, for example, *t*Bu$_3$P or NHC ligands derived from **4**, the dba-*n*,*n*′-Z ligands appear to play a critical role in diminishing the concentration of the catalytically active species "L$_n$Pd^0". In Heck arylation using Fu's conditions, Pd(OAc)$_2$ performed considerably better than [Pd$^0{}_2$(dba-4,4′-H)$_3$]; [Pd$^0{}_2$(dba-3,3′,5,5′-OMe)$_3$] shows slightly lesser activity than Pd(OAc)$_2$ under these specific conditions. A general point therefore emerges from this comparison: for some cross-coupling reactions, certainly not all, Pd(OAc)$_2$ is a superior source of palladium. In due course we will report a full comparative study of Pd(OAc)$_2$, [Pd$^0{}_2$(dba-4,4′-H)$_3$] and [Pd(nbe)$_3$] as palladium sources for cross-coupling reactions (nbe = norbornene).

Under the ligand-free Suzuki–Miyaura cross-coupling conditions, for example, in the absence of an intentionally added donor ligand, it was shown that the dba-*n*,*n*′-Z ligands exhibit a marked affect on catalyst activity, an observation that may be rationalized in part by consideration of the electronic properties of the ligands. It is conceded that the substituent effects here follow a less obvious trend than reactions employing a donor ligand, which is an observation less well understood at this stage. It is clear that dba-*n*,*n*′-Z concentration plays a more crucial role in the ligand-free reactions.

With these results in hand we propose that [Pd^0(dba-3,3′,5,5′-OMe)$_2$] or [Pd$^0{}_2$(dba-3,3′,5,5′-OMe)$_3$] should replace the most commonly used Pd^0 precursor complex, [Pd$^0{}_2$(dba-4,4′-H)$_3$], which are both as easy to prepare.[20] For Buchwald–Hartwig aryl amination reactions, it essentially does not matter what type of Pd^0-precursor complex is used, as the dba-*n*,*n*′-Z ligand is ultimately consumed under the reaction conditions (by base, amine or a combination of both), and as a consequence these ligands do not measurably control the concentration of catalytically active "L$_n$Pd^0" (where L is a monophosphine). We envisage that complexes containing more electron deficient ligands, [Pd$^0{}_2$(dba-4,4′-F)$_3$] and [Pd$^0{}_2$(dba-4,4′-CF$_3$)$_3$] or variants thereof, will be used in specialized applications.

Experimental Section

All solvents were dried using standard procedures prior to use and stored under an argon atmosphere. Nitrogen gas was oxygen-free and was dried immediately prior to use by passage through an 80 cm column containing sodium hydroxide pellets and silica gel. Argon gas was used directly via balloon transfer or on a Schlenk line. TLC analysis was performed routinely using Merck 5554 aluminum backed silica plates or Macherey–Nagel polygram ALOX N/UV$_{254}$ aluminum oxide coated plastic sheets. Compounds were visualized using UV light (254 nm) and a basic aqueous solution of potassium permanganate or acidic DNP (dinitrophenol hydrazine). GC parameters: Analysis was performed using a Varian CP-3800 GC equipped with a CP-8400 Autosampler. Separation was achieved using a DB-1 column (30 m × 0.32 mm, 0.25 μm film thickness) with carrier gas flow rate of 3 mL min^{-1} and a temperature ramp from 50 to 250 °C at 20 °C min^{-1}. The injection volume was 1 μL with a split ratio of 50. The response factors for the internal standard, substrates and products were calculated using an appropriate calibration for this GC and column. The Pd^0 complexes, [Pd$^0{}_2$(dba-*n*,*n*′-Z)$_3$] (*n*,*n*′-Z = 4,4′-CF$_3$; 4,4′-H; 4,4′-MeO; 4,4′-*t*Bu), [Pd^0(dba-*n*,*n*′-Z)$_2$] (*n*,*n*′-Z = 4,4′-CF$_3$; 4,4′-H; 3,3′,5,5′-OMe) and [Pd$^0{}_2$(dba-3,3′-NO$_2$)$_2$], have been reported previously[20,22] [Pd$^0{}_2$(dba-*n*,*n*′-Z)$_3$] (*n*,*n*′-Z = 4,4′-CF$_3$; 4,4′-H; 3,3′,5,5′-OMe) were formed from CH$_2$Cl$_2$ solutions of [Pd^0(dba-*n*,*n*′-Z)$_2$] over 72 h, which were then dried under high vacuum (0.1 mm Hg at 30 °C for 12 h). 1,3-Bis(2,6-diisopropylphenyl)imidazolium chloride (**4**) and tri-*tert*-butylphosphonium tetrafluoroboric acid (*t*Bu$_3$P·BF$_4$) were purchased from Strem Chemicals. HRGC/MS or LCMS was used throughout these studies to confirm the identity and purity of individual reaction components (substrates and products). [Pd^0(dba-3,3′,5,5′-OMe)$_2$], also known as [Pd(dm-dba)$_2$], is available commercially through Sigma-Aldrich (Cat. No. 65 693-3), and is a non-proprietary material.

[Pd$^0{}_2$(dba-4,4′-F)$_3$]: Following the reported procedure,[20] NaCl (1.64 g, 28 mmol) was added to a solution of PdCl$_2$ (2.5 g, 14.6 mmol) in methanol (70 mL) and stirred at ambient temperature under an inert atmosphere for 24 h. It was subsequently filtered through a plug of cotton wool and concentrated in vacuo to approximately half its original volume. The solution was warmed to 60 °C and then 1,5-bis(4′-fluorophenyl)penta-(1*E*,4*E*)-dien-3-one (11.9 g, 44 mmol) was added. The resulting mixture was stirred at 60 °C for 15 min, then sodium acetate (7.23 g, 87.6 mmol) was added, and the reaction cooled gradually to ambient temperature. The mixture was stirred at ambient temperature for 2 h until a dark red precipitate was observed. The precipitate was filtered and washed with methanol (2 × 50 mL), water (2 × 50 mL), and finally acetone (2 × 3 mL). The product was partially dried under suction and then the solid was added to a Schlenk flask which was placed under a flow of nitrogen with stirring overnight. This gave the title compound as a maroon/purple microcrystalline solid (3.81 g, 51.1 %). M.p. 149–151 °C; IR (CH$_2$Cl$_2$): $\tilde{\nu}$ = 1652 m ((ϑ C=O), 1607 vs(ϑ C=C), 1585 (ϑ C=C aromatic), 1567 (ϑ C=C aromatic), 984 cm^{-1} (ϑ CH trans); UV (THF, nm); 226 (π–π*), 337 (n–π*), 536 (d–d); ESI-MS: *m*/*z*: [*M*$^+$] not detected, 775.4 [Pd$_2$dba$_2$Na]$^+$ (70), 881.2 [Pd$_3$dba$_2$Na]$^+$ (54), 987.1 [Pd$_4$dba$_2$Na]$^+$ (100); elemental analysis calcd (%) for C$_{51}$H$_{36}$F$_6$O$_3$Pd$_2$: C, 59.84, H 3.54; found: C 59.53, H 3.78. This compound may be recrystallized from CH$_2$Cl$_2$/Et$_2$O 1:5 to give [Pd$^0{}_2$(dba-4,4′-F)$_3$]·CH$_2$Cl$_2$ (X-ray obtained).[21]

General procedure for Suzuki–Miyaura cross-coupling in the presence of 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (4) (general procedure A): Phenylboronic acid (0.41 mmol), 4-chlorotoluene (0.45 mmol), **4** (0.012 mmol, 3 mol %), [Pd^0(dba-4,4′-H)$_2$] (0.012 mmol, 3 mol %), tetrabutylammonium bromide (0.041 mmol, 10 mol%) and biphenyl (internal standard, 0.04 mmol, 10 mol%) were added to a dry Schlenk tube. The tube was evacuated through three cycles, whilst purging back with nitrogen or argon gas. Dry toluene (2 mL) was then added via cannula and the mixture is stirred magnetically for 5 min (pre-incubation time = 10 min). The mixture was cooled to 0 °C (10 min) and then a solution of KOMe (1.23 mmol, 3 equiv) in dry MeOH (1 mL) was added dropwise over 10 min (total pre-incubation time = 0.5 h for all reactions). The reaction was then warmed to 40 °C over ca. 5 min. The reaction was followed by HRGC analysis after the temperature had reached 40 °C (except for $t=0$). For each analysis point, a 50 μL sample was withdrawn from the reaction mixture by gas-tight syringe and sample was quenched by passage through a small plug of silica (washed with acetone). Several data points were chosen to see whether there was any time dependence effect on post-quenched samples. For this reaction, there was non-observable change in the distribution of starting materials/products which were left standing at room temperature (~23 °C) over 24 h. The spectroscopic data for 4-methylbiphenyl (**3**) was in agreement with the literature.[48]

General procedure for Suzuki–Miyaura cross-coupling under ligand-free conditions: 4-Fluorophenylboronic acid (0.41 mmol), 4-bromo-6-methyl-2-pyrone (0.45 mmol), biphenyl (0.041 mmol, as the internal standard) in 1 M Na_2CO_3 (1.0 mL) and THF (1.5 mL) were degassed via three freeze–pump–thaw cycles. Then the Pd^0 precursor complex (1 mol%) was added under nitrogen gas. The resulting mixture was allowed to stir at 23 °C. Analysis and quenching of the reaction was done in the same way as detailed in procedure A. The spectroscopic data for 4-(4′-fluorophenyl)-6-methyl-2-pyrone (**10**) was in agreement with the literature.[20]

General procedure for α-arylation of esters: The procedure was slightly modified to that reported by Hartwig and co-workers:[32] To a Schlenk tube under an argon atmosphere, containing a magnetic stirrer bar, was added **4** (1.0 mol%) and $[Pd^0_2(dba\text{-}4,4'\text{-}H)_3]$ (0.5 mol%). LiHMDS (1 M solution in hexane) (2.3 mmol, 2.3 mL) was added to a separate reaction flask containing *tert*-butyl acetate (1.1 mmol) which was externally cooled to 0 °C. After 10 min, this solution was cannula transferred into the Schlenk tube containing $[Pd^0_2(dba\text{-}4,4'\text{-}H)_3]$/**4**, and finally bromobenzene (1.0 mmol) and hexadecane (0.1 mmol, as the internal standard) added. The mixture was stirred at 25 °C for 15 h. Samples for HRGC were quenched by addition of aqueous NH_4Cl and the organic components extracted into diethyl ether. The spectroscopic data for *tert*-butyl 2-phenylacetate **14** is in agreement with the literature.[32]

General procedure for Heck arylation reactions (using Schlenk techniques): The procedure was slightly modified to that reported by Fu and co-workers:[33] A Schlenk tube containing a magnetic stirrer bar was charged with Cs_2CO_3 (0.69 mmol), $(tBu)_3P{\cdot}HBF_4$ (0.022 mmol, 3.6 mol%), $[Pd^0_2(dba\text{-}4,4'\text{-}H)_3]$ (3 mol% based on Pd), under an atmosphere of argon. The pre-incubation time was 10 min. 4-Bromoanisole (0.63 mmol), *n*-butyl acrylate (1.2 mmol) and dihexyl ether (0.063 mmol, as the internal standard) were added by microsyringe, followed by dry degassed dioxane (1.0 mL) via cannula transfer. The Schlenk tube was sealed and heated to 120 °C in an oil bath and stirred (600 rpm) for 12 h. Analysis and quenching of the reaction was done in the same way as detailed in procedure A. The spectroscopic data for (*E*)-butyl cinnamate **16** is in agreement with the literature.[33]

General procedure for Heck arylation reactions (for *n*-butyl acrylate): To an automated synthesis robot (ASW 2000, Chemspeed), 32 double jacketed reaction vessels, each equipped with a condenser, were installed. Each vessel was charged with Cs_2CO_3 (0.69 mmol), $(tBu)_3P{\cdot}HBF_4$ (3.6 mol%), the vessels were closed and N_2 applied. The pre-incubation periods may vary by ca. 10 min between reactions. By using the fully automated syringe of the robot, each vessel was charged with dioxane (0.6 mL), 4-bromoanisole (0.63 mmol), $[Pd^0_2(dba\text{-}4,4'\text{-}H)_3]$ as a solution in dioxane (0.021 M, 0.4 mL, 3 mol%; based on Pd), *n*-butyl acrylate (1.2 mmol) and dihexyl ether (0.063 mmol, as the internal standard). All vessels were vortexed (at 600 rpm) and heated to 120 °C for 15 h. At this time, a sample from each vessel was removed (0.1 mL), which was diluted with acetone, and analyzed by HRGC/MS (no further reaction was seen in these samples at 25 °C over several hours by HRGC/MS analysis). An identical procedure was conducted for the other alkenyl substrates, styrene and methyl 2-acetamidoacrylate. The following products exhibited spectroscopic data equivalent to previously reported literature data: (*E*)-4-methoxycinnamic acid *n*-butyl ester,[49] (*E*)-4-fluoro-cinnamic acid *n*-butyl ester,[49] (*E*)-stilbene,[49] (*E*)-2-methoxystilbene,[49] (*E*)-4-fluorostilbene,[49] (*E*)-3-biphenyl-prop-2-enoic acid *n*-butyl ester,[28] 1-phenyl-2-(4′-biphenyl)-(*Z*)-ethene,[50] (*E*)-2-(4′-benzoylphenyl)-1-phenyl-ethene[51] and (*E*)-2-(4′-benzoylphenyl)-prop-2-enoic acid *n*-butyl ester.[52]

Asymmetric intermolecular Heck arylation: Using a slightly modified procedure to that previously reported.[38,39] A Schlenk tube was charged with $[Pd^0_2(dba\text{-}4,4'\text{-}H)_3]$ (3 mol% based on Pd) and (*R*)-BINAP (3 mol%, 3.2 μmol) under inert atmosphere (N_2, back-filled three times), followed by dioxane (2 mL). The mixture was stirred for one hour at 50 °C. After which time, iPr_2NEt, (117 μL, 0.642 mmol), PhOTf (36 μL, 0.212 mmol) and 2,3-dihydrofuran (81 μL, 1.07 mmol) were added. The reaction was stirred at 50 °C under N_2 for 7 d; monitored by HRGC analysis every 24 h (removal of 10 μL aliqouts). The product could be purified by filtration through silica gel, washed with Et_2O (×3) and concentrated in vacuo to give the coupled product (>95% pure by ^1H NMR spectroscopy). The spectroscopic data for the products is in agreement with the literature.[38,39]

General procedure for the Buchwald–Hartwig amination reactions: Note that we did not use a dry-box for the preparation of these reactions as originally reported.[45] We found that it was possible to conduct these reactions using Schlenk techniques providing that the following procedure was followed: To a mixture of $[Pd^0(dba\text{-}4,4'\text{-}H)_2]$ (1 mol%), $tBu_3P{\cdot}HBF_4$ (0.8 mol%) and *t*BuONa (1.5 mmol) in a Schlenk tube was added the aryl bromide (1 mmol) under an inert atmosphere (N_2, back-filled three times), followed by dry degassed toluene (1.5 mL) via glass syringe (aryl halide dissolves the plastic syringes). The mixture was allowed to stir for 15 min, and then hexadecane internal standard (0.1 mmol) and finally aniline (1 mmol) was added (total pre-incubation time = 0.25 h). The progress of the reaction was monitored by HRGC. The product was purified by flash chromatography using ethyl acetate/hexane solvent mixtures. The spectroscopic data for all the amination products is in agreement with the literature.[45]

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