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We Already Know Everything about Oxidative Addition to Pd(o) - Do We?

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Palladium, Oxidative Addition, Mechanism, Bond Activation, Ligand Effects

Abstract The oxidative addition (OA) of organic electrophiles to Pd(0) is a fundamental step in organopalladium chemistry and plays a key role in palladium-catalyzed cross-coupling reactions. This perspective summarizes selected mechanistic studies on the Pd(0)-to-Pd(II) OA process involving organic halides and pseudohalides with a focus on systems relevant to catalytic reactions. The results are organized according to the nature of supporting ligands, extracting general trends and describing the most relevant examples. The formation of active species from pre-catalysts is surveyed, as well as the influence of different species that could be present under catalytic conditions and influence the OA process, offering guidelines to further reinforce the understanding and the improvement of catalytic reactions.

Introduction

Most synthetically useful palladium-catalyzed cross-coupling reactions proceed through a series of steps involving reactive intermediates having a carbon-palladium bond. A common elementary step through which these organopalladium intermediates are formed is the oxidative addition (OA) of organic halides or pseudo-halides to Pd(0) complexes. In this reaction, the formal oxidation state of the metal center is increased by two, thereby generating a Pd(II) complex. The process is often accompanied by an increase of the coordination number and usually delivers a square-planar intermediate with a d^8 electronic configuration.

The efficiency of this fundamental step is one of the key requirements for a successful Pd-catalyzed reaction. Thus, understanding the factors influencing OA is not only of theoretical interest, but is also essential for the rational design and development of catalytic cross-couplings. The variety of systems used in practical organic chemistry such as pre-catalysts, ligands, organic electrophiles, solvents and additives results in a complex mechanistic landscape. In the last decades, in parallel with the development and refinement of synthetic methodology, several mechanistic studies appeared in the field, highlighting fundamental trends and the relevancy of some specifically designed systems.

A variety of techniques has been employed to elucidate the mechanism of OA processes. In particular, electrochemistry appeared early as a suited tool to investigate OA mechanisms, due to the change in the oxidation state of Pd (from Pd⁰ to Pd^{II}) during the reaction.¹ It has been used extensively in combination with multinuclear NMR and molecular modelling at the DFT level to understand the nature of the active species formed under conditions relevant to catalysis, to measure reaction rates, to generate highly reactive or unstable species,

and to comprehend the effect of additives present under catalytic conditions.

One of the most significant outcomes of these studies is the crucial role played by the pre-catalytic steps, *i.e.* the formation of active Pd(0) species from pre-catalysts, in controlling the speciation of the catalysts under reaction conditions. Several recent studies have highlighted the structural complexity obtained even for supposedly simple catalytic systems.^{2,3} Thus, Pd(0) complexes speciation as well as formation mechanism(s) are discussed when necessary to explain the observed reactivity.

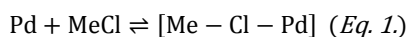
The goal of this review is to summarize and outline in a rational fashion the main results regarding the OA of organic electrophiles to Pd(0) complexes, under conditions relevant for catalytic reactions, to benefit the development and the optimization of Pd-based catalytic processes. Pd chemistry is a unique source of inspiration for the current rise of first-row-metal catalysis. The variety of proposed mechanisms, and the number of factors influencing them, highlight the necessity of an in-depth mechanistic understanding to develop efficient catalytic systems and provide inspiration to overcome current challenges in reactivity.

OA processes involving other oxidation numbers, in particular, Pd(II)-to-Pd(IV),^{4,5} and the reactivity of palladium nanoparticles and heterogeneous catalysts are beyond the scope of the present work. Results are presented here by families of ligands since the nature of the ligand itself arguably has the most important on the OA process. OA to both mononuclear and polynuclear Pd complexes is covered.

1. Insights from OA to a Ligandless Isolated Pd Atom

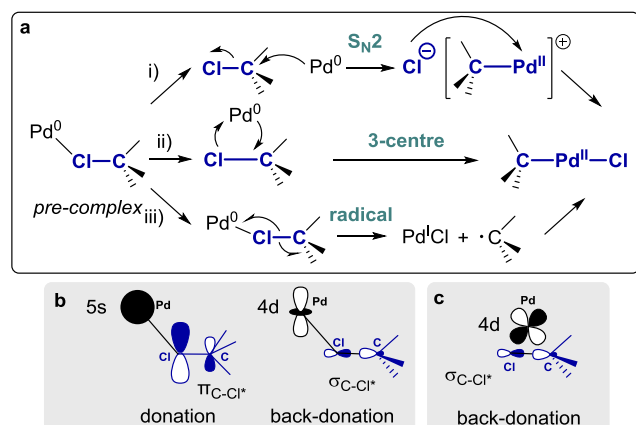
The OA of a ligandless single Pd atom in various bonds was thoughtfully studied by Bickelhaupt and co-workers using simulations at the DFT level.⁶⁻¹² While the electronic proper-

ties of this model are far away from ligated Pd(0) present under typical catalytic conditions, it is interesting to understand the intrinsic behaviour of a Pd atom before tuning its reactivity *via* the addition of ligand. We will focus herein on the OA of a Pd atom to MeCl (Equations 1-2).⁶



Before OA, the Pd atom interacts with the chlorine atom of chloromethane through a halogen-bond-like interaction (Equation 1).⁶ This interaction can be decomposed mainly in two major contributions: *i.* donation from the C-Cl lone pair lobe localized on Cl $\pi_{\text{C-Cl}}^*$ to the vacant $5s$ orbital of Pd(0) and *ii.* back-donation from the d_{z^2} orbital of Pd to the C-Cl antibonding $\sigma_{\text{C-Cl}}^*$ orbital localized over the C-Cl bond (Scheme 1b). The combination of both interactions leads to an elongation of the C-Cl bond and can be seen as a pre-activation step. Such adducts are usually impossible to isolate although one was detected using ion-trap mass spectroscopy with a specifically designed phosphine ligand $[\text{PPh}_2(m\text{-C}_6\text{H}_4\text{SO}_3)]^-$.¹³

Three different mechanisms were proposed for the OA of Pd atom to a C-Cl bond (Equation 2, Scheme 1):⁶ *i.* a $\text{S}_{\text{N}}2$ type mechanism through a backside approach, *ii.* a 3-centered concerted insertion involving a side attack or *iii.* a radical process. While the 3-centered path is lower in energy in vacuum for aliphatic halides, increasing solvent polarity favors a $\text{S}_{\text{N}}2$ mechanism.⁶ This is to be expected since a $\text{S}_{\text{N}}2$ mechanism involves the formation of an ion pair.¹⁴



Scheme 1. a. General Mechanisms for OA to Pd; b. Frontier orbitals two-electron interactions between chloromethane and atomic Pd(0) in the pre-OA complex; c. Main two-electron interaction in the transition state of OA of chloromethane to atomic Pd(0). Adapted from reference 6. Copyright 1995 American Chemical Society.

Going from aliphatic to aromatics halides, OA is facilitated, and the 3-centered mechanism becomes the most favorable one. The 3-centered mechanism takes place through back-donation from the $4d$ to the $\sigma_{\text{C-Cl}}^*$ leading to the breaking of the C-Cl bond itself (Scheme 1c).⁶ The lower HOMO-LUMO gap of the aryl electrophile compared to the alkyl ones, is favoring additional donation and back-donation from the aromatic-ring-located orbitals to Pd(0).¹⁵ In addition, the electronic properties of the electrophile and of the metal centre are not the only ones to account for observed reactivity trends. Indeed, the influence of the balance between steric repulsion and attractive weak interactions on the OA of a series of substituted aliphatic C-X (X = C, H) on Pd(0) was recently reported by

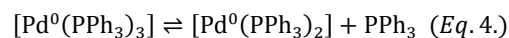
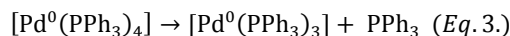
the group of Bickelhaupt.¹⁶ For C-C bonds, the OA energy barriers increase along with the degree of substitution of the carbon atoms, while the reverse trend is observed for C-H bond activation. This apparent discrepancy in reactivity trend was explained in terms of differential steric repulsion between the activated fragments *vs* the catalyst and the substrate.

2. OA to PPh_3 -Ligated Pd(o)

Triphenylphosphine has a historical importance in the field of organopalladium chemistry since it was one of the first and most popular ligands for catalytic applications. Consequently, early investigations mainly focused on PPh_3 -ligated Pd complexes, and the results of these studies highlighted trends that serve as a model and can possibly be extended to more complex systems employed in present-day catalysis.

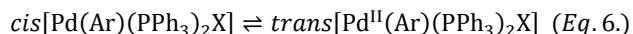
2.1. Addition of Aryl Halides to PPh_3 -Ligated Pd(o)

The first complexes of the type $\text{trans}[\text{Pd}^{\text{II}}(\text{Ar})(\text{PPh}_3)_2\text{X}]$, obtained from the reaction of $[\text{Pd}^0(\text{PPh}_3)_4]$ with an aryl halide ArX , were isolated by Fitton in 1968.¹⁷⁻¹⁹ In solution, $[\text{Pd}^0(\text{PPh}_3)_4]$ dissociates spontaneously to form $[\text{Pd}^0(\text{PPh}_3)_3]$ (Equation 3). More unsaturated $[\text{Pd}^0(\text{PPh}_3)_2]$ and $[\text{Pd}^0(\text{PPh}_3)]$ complexes could not be detected by ^{31}P NMR even at low temperature.²⁰



Ab initio molecular dynamics (AIMD) calculations conducted in a solvent cage by Vidossich, Ujaque and Lledos indicate that $[\text{Pd}^0(\text{PPh}_3)_2(\text{toluene})]$, $[\text{Pd}^0(\text{PPh}_3)_2]$ and $[\text{Pd}^0(\text{PPh}_3)(\text{toluene})]$ are all thermodynamically accessible in toluene, while the formation of “truly” monoligated Pd(0) is very unlikely.²¹

Based on kinetic evidence obtained from amperometric measurements, Fauvarque and co-workers proposed $[\text{Pd}^0(\text{PPh}_3)_2]$ to be the active species in OA.²² Addition of excess PPh_3 to the reaction mixture slows the reaction down, consistently with phosphine dissociation being required for the OA to proceed (Equation 5). Since only the *cis* OA product $\text{cis}[\text{Pd}^{\text{II}}(\text{Ar})(\text{PPh}_3)_2\text{X}]$ is formed through the concerted insertion of Pd into the C-X bond, then, isomerization should take place to lead to the more stable $\text{trans}[\text{Pd}^{\text{II}}(\text{Ar})(\text{PPh}_3)_2\text{X}]$ (Equation 6). This step was studied in detail and careful kinetic analyses revealed four different bimolecular mechanisms involving autocatalytic processes and solvent-assisted steps.²³



Eyring parameters for the OA of $[\text{Pd}^0(\text{PPh}_3)_3]$ to PhI were obtained in THF ($\Delta H^\ddagger = 18.4 \text{ kcal mol}^{-1}$ and $\Delta S^\ddagger = 3.1 \text{ cal mol}^{-1} \text{ K}^{-1}$)²² and in toluene ($\Delta H^\ddagger = 17.9 \text{ kcal mol}^{-1}$ and $\Delta S^\ddagger = 1.7 \text{ cal mol}^{-1} \text{ K}^{-1}$).²⁴ The similarity of the values obtained in both solvents is consistent with a low-polarity transition state and thus with a concerted mechanism.²⁴ The low value of activation entropy was interpreted as the overlay of the positive entropy variation due to the PPh_3 dissociation (Equation 4) and of the negative activation entropy related to the associative reaction (Equation 5). Calculations performed at the DFT level confirmed that a 3-centered concerted OA to $[\text{Pd}^0(\text{PPh}_3)_2]$ was favored for aryl iodides,^{13,25} while further

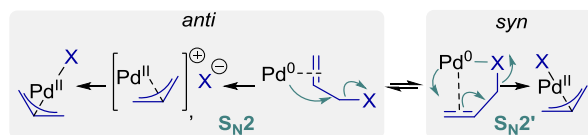
phosphine dissociation to form $[\text{Pd}^0(\text{PPh}_3)]$ was suggested for aryl bromides and chlorides, based on mass spectroscopy using a sulfonated derivative of PPh_3 as a ligand, and ^{13}C kinetic isotopic effects.²⁶ The additional back-donation from $\text{Pd}(0)$ to the antibonding π^* orbitals of aromatic halides also facilitates the OA of aryl halides relative to the one alkyl halides (Scheme 1).¹⁵

The reactivity ranking for aryl-halides is $\text{ArI} > \text{ArBr} \approx \text{OTf} > \text{ArCl}$ (with $>$ meaning “reacts faster than” and \approx “reacts similarly than”).^{19,27-30} Electronic effects were also investigated both experimentally and computationally. In general, electron-poor aromatic halides react faster than electron-rich ones.^{19,22,24} Hammett correlations show similar slope values of $\rho = 2.3$ in toluene²⁴ and $\rho = 2.0$ in THF.²² These results are consistent with a negative charge developing on the aromatic ring in the transition state, as also confirmed by calculations.³¹ This effect is only slightly more pronounced for aryl triflate derivative in DMF with a slope of $\rho = 2.5$.²⁹ Electron density on the Pd center can be tuned by changing the *para*-substituent Z on the $\text{P}(p\text{-Z-C}_6\text{H}_4)_3$ ligand as investigated by Amatore and Jutand on $\text{Pd}(0)$ -complexes prepared from tris(dibenzylideneacetone)dipalladium(0) $[\text{Pd}_2(\text{dba})_3]$.³² The Hammett plot of the apparent rate constant of OA shows a bell-shaped profile due to the competition between dba substitution by $\text{P}(p\text{-Z-C}_6\text{H}_4)_3$, which is favored for electron-poor phosphine, and OA which is facilitated by electron-rich phosphines.

2.2 OA of Alkyl and allyl Halides to PPh_3 -Ligated $\text{Pd}(0)$

OA of alkyl halides to $\text{Pd}(0)$ is slower than that of aryl halides.^{15,33} This reluctant behavior leads to some difficulties in developing new catalysts for $\text{sp}^3\text{-sp}^3$ coupling.^{34,35} Ariafard and Lin explained this different compartment using MO arguments considering a three-centered concerted mechanism.³⁶ Since concerted insertion is disfavored in the case of alkyl halides, a $\text{S}_{\text{N}}2$ mechanism becomes possible as validated experimentally and computationally.^{37,38} This change in mechanism lead to different selectivity for sp^2 vs sp^3 arylation depending on the size of the phosphine used (see section 4).

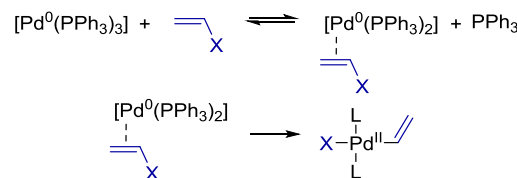
The Pd-catalyzed allylation of nucleophiles (the Tsuji-Trost reaction) is a widely used transformation, including in asymmetric synthesis. The stereochemistry is well-controlled during OA where the addition occurs *via* the attack of the Pd at one of the terminal C of the allyl (Scheme 2). Addition to the allyl central C atom was also reported and result in the formation of a cyclopropane intermediate.³⁹ The selectivity obtained is highly dependent on the reaction conditions, particularly on the choice of the nucleophile, the ligand, the solvent, and on the presence of additives. Electron-poor $\text{Pd}(0)$ sources, such as $[\text{Pd}_2(\text{dba})_3]$, used in nonpolar solvents favors a *syn* selective OA, while the use of electron-rich ligands and polar solvents promotes the *anti* addition (Scheme 2).^{40,41}



Scheme 2. Mechanisms of OA of allylic halide to PPh_3 -ligated $\text{Pd}(0)$ complex. Adapted from reference 40. Copyright 1992 American Chemical Society.

This selectivity was rationalized by Thiel using DFT calculation.⁴² *Anti* OA follows an $\text{S}_{\text{N}}2$ type mechanism with synchronized substitution of the halide by the Pd atom. For *syn* addition Pd is adding to the C in the β -position ($\text{S}_{\text{N}}2'$ -type). The *syn* pathway exhibits strong donation of the *p* orbital of the halogen atom to $\text{Pd}(0)$ which is favored for electron deficient $\text{Pd}(0)$.

2.3 OA of Vinyl Halides to PPh_3 -Ligated $\text{Pd}(0)$

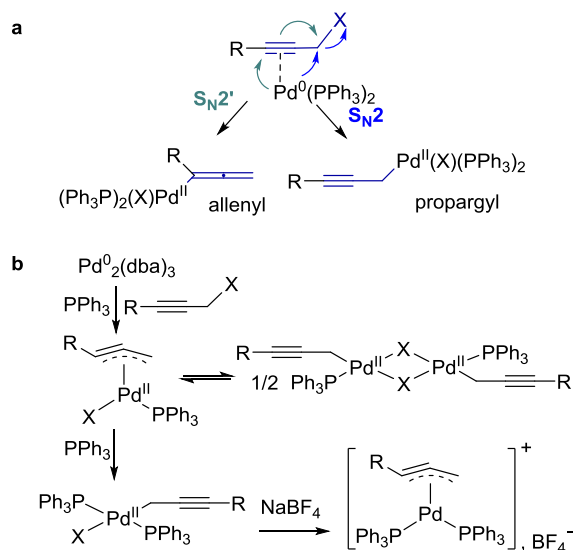


Scheme 3. Mechanism of the OA of vinyl halides to $[\text{Pd}^0(\text{PPh}_3)_3]$. Adapted from reference 43. Copyright 2003 American Chemical Society.

The OA of vinyl halides to $[\text{Pd}^0(\text{PPh}_3)_3]$ takes place after exchange of one phosphine ligand with the vinyl to form a π -complex with $\text{Pd}(0)$ (Scheme 3).⁴³ In general, vinyl derivatives undergo OA faster than the analogous aryl derivatives.⁴³ Although the π -complex cannot be isolated with PPh_3 , its formation could be evidenced for the vinyl chloride using dppf (1,1'-bis(diphenylphosphino)ferrocene) as a ligand (see section 5).⁴⁴ The same type of intermediate has been proposed for the OA of allyl and propargyl halides.⁴⁵ Since the electrophile may also act as a ligand in this case, the use of a phosphine ligand is not always required and may even be detrimental (see section 3.2).

2.4 OA of Propargyl Halides to PPh_3 -Ligated $\text{Pd}(0)$

OA of propargyl halides to a metal center may lead to the formation of η^1 or η^3 propargyl or allenyl complexes (Scheme 4a).^{46,47} Upon OA to $[\text{Pd}^0(\text{PPh}_3)_4]$ only the allenyl product is obtained.^{48,49} This product could be obtained either directly via $\text{S}_{\text{N}}2'$ mechanism or through $\text{S}_{\text{N}}2$ and subsequent isomerization. The propargyl and allenyl complexes are expected to be in rapid equilibrium.⁵⁰ In the case of the parent halogenoallenes, a $\text{S}_{\text{N}}2'$ mechanism has been proposed based on the stereoselectivity of the reaction.⁵¹ The η^3 -propargyl products can be obtained either when only one equivalent of phosphine is used,⁵² or if the OA product is cationized by a borate salt (Scheme 4b).^{47,53} Kinetic constants for the $\text{S}_{\text{N}}2$, $\text{S}_{\text{N}}2'$ and isomerization pathways have been reported by Canovese using bidentate ligands (see section 5).^{54,55}



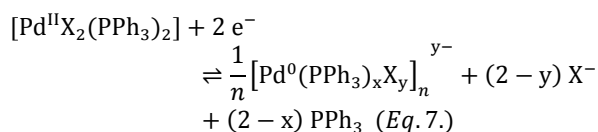
Scheme 4. Mechanisms of Pd(0) OA to propargylic halides. Adapted with permission from reference 47 and 53. Copyright 1995 Elsevier Science S.A.

3. Agonistic and Antagonistic Effects

3.1 Salt and Solvent Effects on OA to Pd(o)

The addition of halide salts (LiCl, LiBr, LiI, Bu₄NI, Bu₄NF, ZnCl₂, ...) often has a positive impact on the yields of Pd-catalyzed cross-couplings of aryl triflates,⁵⁶⁻⁵⁹ and allows to decrease the temperature required for some Heck couplings (e.g. *n*-Bu₄NCl, the so-called "Jeffery conditions").⁶⁰ Salt addition has successfully been used in order to promote the reactivity of less reactive bonds.⁶¹ Schoenebeck and collaborators have reported the effect of salt addition and solvent polarity on the chemoselectivity of Suzuki-coupling using polyhalogenated derivatives.⁶²

It was proposed that these effects could be due to the formation of anionic Pd(0) intermediates. Such anionic Pd(0) species of the type [Pd⁰(X)_x(PPh₃)₂]_n^{x-} (X = Cl, Br, OAc) formed either by chemical reduction using an organolithium reagent,⁶³ [Pd⁰(OAc)₂(PPh₃)₂] in the presence of a base,^{28,30,64,65} or by electrochemical reduction⁶⁶⁻⁷⁰ have been reported. The electro-generation of Pd(0) (Equation 7) directly from a Pd(II) precursor is a powerful method to assess the activity of transient Pd(0) complexes, within a controlled chemical environment (*i.e.* in the absence of added reducing agent).¹ Electrochemical reduction of [Pd^{II}(X)₂(PPh₃)₂] (X = Cl, Br) leads to the formation of three anionic Pd(0) halide complexes in equilibrium (Table 1).^{67,71}



Iodobenzene performs OA to a mixture of electrogenerated anionic Pd(0) from 25 (X=Br) to 33 (X=Cl) time faster than to [Pd⁰(PPh₃)₄] (Table 1).^{67,71}

Table 1. Rate constants for the OA of PhI to the different active electrogenerated Pd(0) complexes (starting from [Pd^{II}(PPh₃)₂X₂]). Constants are given in M⁻¹ s⁻¹. Adapted from reference 67. Copyright 1991 American Chemical Society.

	A	B	C
	$[\text{Ph}_3\text{P}-\text{Pd}^0-\text{X}]^-$	$[\text{Ph}_3\text{P}-\text{Pd}^0-\text{X}-\text{Pd}^0-\text{PPh}_3]^{2-}$	$[\text{Ph}_3\text{P}-\text{Pd}^0-\text{X}]^{2-}$
X = Cl	-	$k_B = 10^4$	72 ± 3
X = Br	500 ± 10	-	50 ± 5

Global reaction order seems to indicate that species (A) is the relevant one when X = Cl while (B) would be the major and most active species in the case of X = Br. The use of electro-generated anionic Pd(0) also allowed to investigate cation effects on OA.⁶⁹ The addition of Li⁺ or Zn²⁺ salt allows to approximately triple the rate of OA compared to the non-coordinating *n*-Bu₄N⁺ counter-cation (Table 1).⁶⁷ Conversely, a detrimental effect of ZnCl₂ was suggested by recent DFT calculations on OA of vinyl bromine to [Pd⁰(PMe₃)₂].⁷² Note that the direct addition of *n*-Bu₄NCl to [Pd⁰(PPh₃)₄] conversely slows down the rate of the OA compared to [Pd⁰(PPh₃)₄] alone. This effect originates from the excess of ligand used prohibiting the formation of coordinatively unsaturated Pd(0) intermediate.²⁵

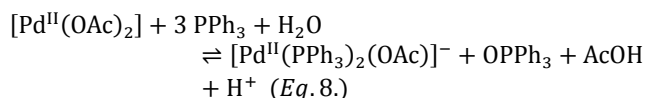


Table 2. Apparent rate constants (k , M⁻¹ s⁻¹) for the OA of various PPh₃-ligated Pd complexes to PhI. Reproduced with permission from reference 69. Copyright 1999 Elsevier Science S.A.

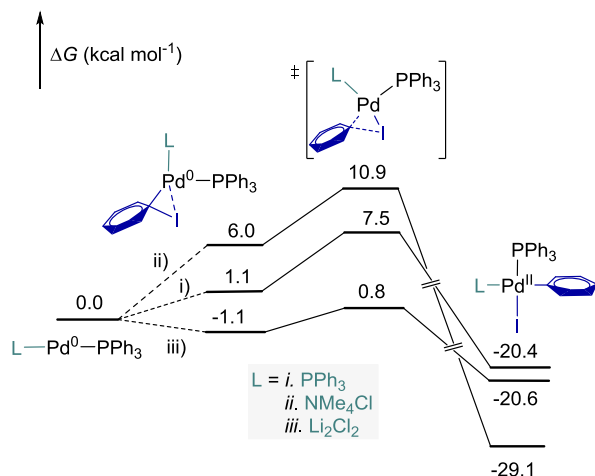
Pd(0) Precursor	Proposed major complex	k (M ⁻¹ s ⁻¹)
[Pd ⁰ (PPh ₃) ₄]	[Pd ⁰ (PPh ₃) ₃]	16
[Pd ^{II} (Br) ₂ (PPh ₃) ₂] + 2 e ⁻	[Pd ⁰ (PPh ₃) ₂ Br] ⁻	400
[Pd ^{II} (Cl) ₂ (PPh ₃) ₂] + 2 e ⁻	[Pd ⁰ (PPh ₃) ₂ Cl] ⁻	530
[Pd ^{II} (Cl) ₂ (PPh ₃) ₂] + 2 e ⁻ + Li ⁺	Li ⁺ , [Pd ⁰ (PPh ₃) ₂ Cl] ⁻	1320
[Pd ^{II} (Cl) ₂ (PPh ₃) ₂] + 2 e ⁻ + Zn ²⁺	ZnCl ⁺ , [Pd ⁰ (PPh ₃) ₂ Cl] ⁻	1480
[Pd ^{II} (OAc) ₂] + 3 PPh ₃	[Pd ⁰ (PPh ₃) ₂ OAc] ⁻	65
[Pd ^{II} (OAc) ₂] + 3 PPh ₃ + 3 NEt ₃	H ⁺ , [Pd ⁰ (PPh ₃) ₂ (OAc)] ⁻	140

The combination of [Pd^{II}(OAc)₂] with *n* equivalents of PPh₃ (*n* ≥ 2) is commonly used to access *in situ*-generated Pd(0) in practical applications.⁶⁴ Reduction of Pd(II) takes place through inner-sphere nucleophilic attack of the acetate ligand on one of the phosphines leading to the formation of an anionic Pd(0)-acetate complex, along with a phosphonium species [Ph₃P-OAc]⁺ that is subsequently hydrolyzed to PPh₃O and AcOH (Equation 8).²⁸

The anionic complex $[\text{Pd}^0(\text{PPh}_3)_2(\text{OAc})]^-$ reacts with PhI roughly 4 times faster (Table 2) than $[\text{Pd}^0(\text{PPh}_3)_4]$ and $[\text{Pd}^{\text{II}}(\text{Ph})(\text{OAc})(\text{PPh}_3)_2]$ is formed quantitatively.²⁸ A mixture of AcO^-/AcOH proved to increase even more than AcO^- the rate of OA. This was suggested to originate from a specific proton effect.⁶⁹

The molecular explanation of this anion effect has been the object of a lively debate: the initially proposed pentacoordinate anionic Pd intermediate⁶⁸ accounting for the increased activity has been clearly excluded by DFT calculations.⁷³⁻⁷⁶ Conversely, several scenarios are still proposed involving either *i.* OA to a di-coordinated anionic complex $[\text{Pd}(\text{PMe}_3)\text{X}]^-$,^{74,77} or *ii.* a charge effect due to the presence of the anion X^- in the second coordination sphere of Pd.^{73,74,78,79}

The effects of NMe_4Cl and LiCl on the OA of PhI to $\text{Pd}^0(\text{PPh}_3)_2$ were computationally studied by the group of Perrin and Payard using DFT.²⁵ It was found that chloride favors the dissociation of PPh_3 leading to a mixture of mono-nuclear and di-nuclear (see section 6) Pd(0) complexes (Scheme 5). Additionally, coordination of NMe_4Cl and LiCl improves the ability of Pd(0) to insert into the C-I bond compared to $\text{Pd}^0(\text{PPh}_3)_2$. However, NMe_4Cl decreases the affinity of Pd(0) towards PhI, leading to a similar overall free energy of activation compared to neutral $\text{Pd}^0(\text{PPh}_3)_2$. On the contrary, the presence of LiCl improves the affinity of Pd(0) towards PhI (Scheme 5) leading to an overall nearly barrierless OA.



Scheme 5. Gibbs energy (kcal mol^{-1}) profiles for the OA of PhI to *i.* $[\text{Pd}^0(\text{PPh}_3)_2]$, *ii.* $(\text{NMe}_4)[\text{Pd}^0(\text{PPh}_3)_2\text{Cl}]$ and *iii.* $\text{Li}_2[\text{Pd}^0(\text{PPh}_3)_2\text{Cl}_2]$ complexes. Adapted from reference 25. Copyright 2022 American Chemical Society.

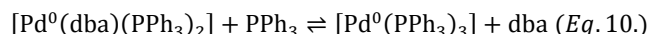
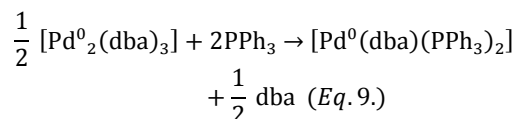
To the best of our knowledge, a study that compares the impact of salts on the kinetics of the OA step is still missing. This will contribute elucidating how salts can modulate the energy barrier, and consequently enable the design of more efficient catalytic cycles. Alternatively, the understanding of salt effects on the OA step may be also further reinforced by *ab initio* molecular dynamics, such as metadynamics⁸⁰⁻⁸³ or by data-driven methods similar to the ones recently used by the groups of Leitch and Doyle.^{84, 85}

In addition to salts, solvents impact the mechanism of the OA catalyzed by Pd(0). Though the molecular understanding of solvent effects can be difficult to capture, Fairlamb proposed an extensive critical review of solvent effects in palladium catalyzed cross-coupling reactions.⁸⁶ As a representative illustration, the chemoselectivity of OA (C-Cl vs C-OTf) mediated

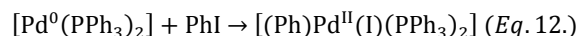
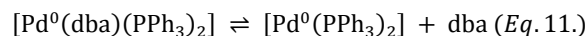
by the bulky and electron-rich $\text{Pd}^0\text{P}(t\text{Bu})_3$ can be oriented depending on the polarity of the solvent, as reported by Neufeldt.⁸⁷

3.2 Alkenes as Ligands

Alkenes moieties are frequently present in cross-coupling reactions, either as substrates, like in Heck couplings,⁸⁸ or as ligands for pre-catalyst, *e.g.* the very popular $[\text{Pd}^0_2(\text{dba})_3]$ precursor. Alternatively, to the *in-situ* reduction of Pd(II) precursors, PPh_3 -ligated Pd^0 may be obtained by mixing air-stable $[\text{Pd}^0_2(\text{dba})_3]$ with PPh_3 . Addition of two equivalents per Pd(0) of PPh_3 on $[\text{Pd}^0_2(\text{dba})_3]$ leads to the formation of the mixed complex $[\text{Pd}^0(\text{dba})(\text{PPh}_3)_2]$ (Equation 9).⁸⁹ Upon addition of more than two equiv *per* Pd, dba is partially displaced and a mixture of $[\text{Pd}^0(\text{dba})(\text{PPh}_3)_2]$ and $[\text{Pd}^0(\text{PPh}_3)_3]$ is obtained (Equation 10, equilibrium constant $K = 0.18$).



The presence of both additional dba and PPh_3 slows down the OA of PhI, consistently with $[\text{Pd}^0(\text{PPh}_3)_2]$ being the active form of Pd(0) (Equations 11 and 12).^{89,90}



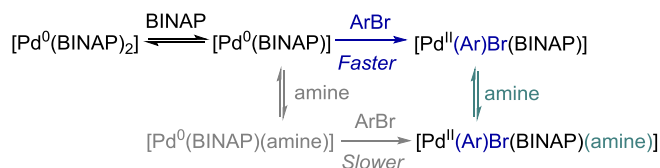
This deactivation can be used to tune the activity of the catalyst by slowing down the OA kinetics. In general, alkenes are known to reduce the rate of OA by competing the binding of the substrate.^{65,91,92} This effect has been evidenced not only with PPh_3 , but also with other ligands on Pd(0) such as diphosphines (see section 5),⁹³ mixed phosphine-amine ligands,⁹⁴ carbon monoxide (see section 6.1) and arsines.⁹⁵ One possible way to counter-balance the effect of alkenes on OA is to add a Lewis acid that competitively coordinate the alkene.⁹¹

3.3 OA to Nitrogen-Ligated Pd(0)

Amines and nitrogen-containing heteroarenes are widely used in cross-coupling reactions, either as substrates in Buchwald-Hartwig aminations^{96,97} and in C-H activation reactions, or as bases as in the case of the Suzuki-Miyaura⁹⁸ and Sonogashira cross-couplings⁹⁹ or as ligands. Additionally, primary and secondary amines can also play the role of reducing agents to generate Pd(0) from the Pd(II) pre-catalyst.^{28,30,64,70,100}

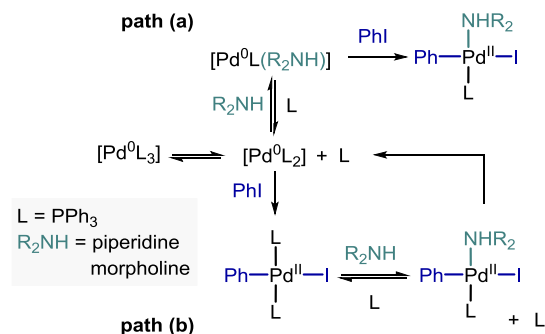
In the context of the Buchwald-Hartwig amination, there has been a lively debate about whether amines can coordinate to Pd(0) and facilitate OA or not. In a series of articles,¹⁰¹⁻¹⁰⁴ Hartwig, Blackmond and Buchwald studied the kinetics of the OA of aryl bromides to diphosphine-ligated Pd. Based on kinetic studies, the $[\text{Pd}^0(\text{BINAP})_2]$ -catalyzed amination was proved to be first-order in bromoarene and inverse first-order with respect to excess BINAP (BINAP = 2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene).¹⁰¹ On the other hand, the concentration of amine has no effects on the reaction kinetics.¹⁰² Overall, the experimental evidences support that $[\text{Pd}^0(\text{BINAP})]$ generated from BINAP dissociation from

$[\text{Pd}^0(\text{BINAP})_2]$ performs OA and that amine coordination is not involved in this first step (Scheme 6).¹⁰³



Scheme 6. OA of ArBr to Pd(0) (BINAP) generated from Pd⁰ (BINAP)₂. Adapted from reference 103. Copyright 2006 American Chemical Society.

Conversely, in the case of monophosphines, several reports point out that nitrogen-coordinated Pd could be more active toward OA than phosphine-coordinated Pd complexes. In 2000, Buchwald reported that Pd complexes supported by the monophosphine ligands (*o*-biphenyl)P(*t*Bu)₂ and (*o*-biphenyl)P(Cy)₂ are efficient in catalytic amination reactions of aryl chlorides, bromides, and triflates, in a large scope.¹⁰⁵ Then, using Pd^{II}(OAc)₂ as a precatalyst, they further investigated the role played by amines on the kinetics of coupling between *p*-chlorotoluene and morpholine.¹⁰⁶ In this study, a series of monodentate biarylphosphines were used in combination with NaOtAm. It was found that the concentration of the amine modulates the steady-state concentration of the Pd based active species. This parallels the influence of the PPh₃ to Pd ratios on the C2 vs C4 regioselectivity of the 2,4-dibromopyridine OA as reported by Fairlamb.³ Though the reactivity and selectivity trends are discussed in terms of ligand's hindrance, the propensity of Pd to form clusters under the reaction conditions has not been yet mechanistically addressed, to the best of our knowledge.



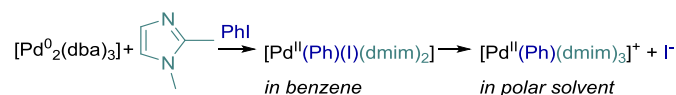
Scheme 7. Mechanism for the OA of PhI to the Pd(0) complex generated from [Pd⁰(PPh₃)₃] in the presence of a secondary amine. Adapted with permission from reference 99. Copyright 2007 WILEY-VCH Verlag GmbH & Co.

Later on, in 2007, Jutand⁹⁹ studied the role of amines in the OA step of Sonogashira cross-couplings and reported that the rate of iodobenzene OA to Pd⁰L₄ (L = PPh₃, AsPh₃) in the presence of piperidine or morpholine was faster than in the absence of amine. Two mechanisms that contribute to the overall mechanism were proposed and are illustrated in Scheme 7.

In path (a), substitution of a phosphine by an amine occurs prior to OA.¹⁰⁷ while in path (b), the reaction starts with OA of PhI to Pd⁰L₂ to form the *trans*-[Pd^{II}(I)(Ph)(L)₂], followed by phosphine substitution by the amine to give [Pd^{II}(I)(Ph)(L)(R₂NH)]. The released phosphine can then react with Pd⁰L₂ to regenerate the unreactive Pd⁰L₃. Each pathway contribution was detected depending on the amine concentra-

tion. Path (a) is faster at the beginning of the reaction but its rate decreases relative to the one of path (b) over time.

When studying the Pd-catalyzed C-H activation of imidazole, Perego, Grimaud and Bellina evidenced that *i.* the reaction proceeds through imidazole-ligated intermediates, and *ii.* the addition of PPh₃ slows down the OA kinetics (Scheme 8).¹⁰⁸ Additionally, they showed that PPh₃-ligated aryl-Pd species are not able to perform the C-H functionalization of imidazole, while novel imidazole-coordinated organo-Pd complexes undergo C-H functionalization, even at room temperature. They studied OA of aryl halides with dmim-ligated (dmim = 1,2-dimethyl-1*H*-imidazole) Pd(0) species on the model system [Pd₂(dba)₃]/dmim, the corresponding product [Pd^{II}(Ph)(dmim)₃I] was isolated and characterized (Scheme 8). More recently, based on a joint computational and experimental study, they reported a cooperative mechanism in which two nitrogen-ligated Pd(0) centres promote the OA of aryl iodide (see section 7.2 for detailed discussion).¹⁰⁹



Scheme 8. OA of PhI to dmim-ligated Pd(0) (dmim = 1,2-dimethyl-1*H*-imidazole). Adapted with permission from reference 108. Copyright 2016 WILEY-VCH Verlag GmbH & Co.

4. Hindered Monophosphine

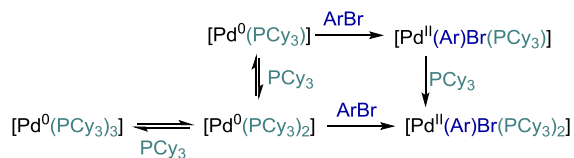
The use of electron-rich and sterically-demanding phosphines, that have a cone angle larger than 180° such as P*t*Bu₃, allowed developing cross-couplings and amination reactions with less reactive partners such as aryl chlorides and aryl tosylates and was recently reviewed in details by Colacot and co-workers.¹¹⁰ In modern cross-coupling chemistry, hindered monophosphine ligands are often employed in a variety of transformations involving complex polyfunctional substrates and are also a usual choice when the reduction of Pd loading is desired, such as for the large-scale manufacturing of pharmaceutical intermediates.

The OA of alkyl halides to Pd(0) complexes ligated by hindered monophosphines was studied in detail by Fu and co-workers.¹¹¹ The OA is very efficient with alkyl iodides (the reaction can be done at -60°C) and alkyl bromides (the reaction occurs at 0°C) but it requires temperatures up to 60°C for alkyl tosylates and chlorides. OA is highly sensitive to the steric hindrance of the electrophile. For instance, linear primary alkyl derivatives react five times faster than branched alkyl halides, twenty times faster than β-substituted ones and no OA was observed for α-substituted substrates. Among the various phosphines tested, P*t*Bu₂Me and PCy₃ are more efficient than P*t*Bu₂Et and no reaction was observed with P*t*Bu₃. These experimental data were correlated with activation parameters determined by calculations performed at the DFT level, which demonstrated that the approach of the alkyl halide to the conformer of lower energy is impeded for [Pd⁰(P*t*Bu₂Et)₂] relative to [Pd⁰(P*t*Bu₂Me)₂]. The reaction turned out to proceed through a S_N2-type reaction with [Pd⁰L₂] with no effect of added phosphine on the kinetics of the reaction. Accordingly, polar solvents favor the reaction.

Related studies focused on aromatic halides have been reported by several groups. Indeed, the use of P*t*Bu₃ paved the way to the activation of aryl chlorides¹¹²⁻¹¹⁴ through an oxida-

tive addition that proceeds from the monoligated $[\text{Pd}^0\text{L}]$. The OA with PCy_3 -ligated $\text{Pd}(0)$ was studied by Baird and co-workers.¹¹⁵ The kinetics performed in non-polar solvents demonstrated that both $[\text{Pd}^0(\text{PCy}_3)_2]$ and $[\text{Pd}^0(\text{PCy}_3)]$ are involved in the OA. However, addition of an extra PCy_3 resulted in the decrease of the reaction rate due to a lower concentration of the very active monoligated $[\text{Pd}^0\text{L}]$ complex and to the formation of the poorly reactive $[\text{Pd}^0(\text{PCy}_3)_3]$.

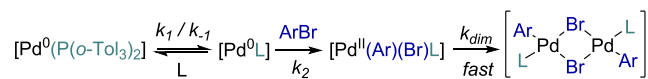
The efficiency of $\text{P}(t\text{Bu})_{3-n}(\text{Cy})_n$ as ligands was investigated with aryl iodides.¹¹⁶ The increase of the steric demand of the ligand disfavors the OA with the *bis*-coordinated Pd species in favor of the 12 electron $[\text{Pd}^0\text{L}_2]$ complex. Indeed, $[\text{Pd}^0\text{L}_2]$ is operative for PCy_3 and $\text{P}(t\text{Bu})\text{Cy}_2$ albeit at a slower rate in this case and $[\text{Pd}^0\text{L}]$ is the active species for $n < 2$. These results were further corroborated by computational studies.^{76,117,118} The identity of the halide influences both the nature of the product formed after OA and the mechanism of the OA. Indeed, in a systematic study, Hartwig and co-workers have shown that with PCy_3 , the OA gives the expected $[\text{Pd}^{\text{II}}(\text{Ar})(\text{X})\text{L}_2]$ complex, whereas the dimeric species $[\text{Pd}^{\text{II}}(\text{Ar})(\text{X})\text{L}]_2$ was formed when using a more sterically hindered ligand such as $\text{P}(t\text{Bu})_2\text{Cy}$ or $\text{P}(1\text{-Ad})(t\text{Bu})_2$.¹¹⁹ PtBu_3 behaves differently as the dimer was observed for chlorides, while tricoordinated monomers were isolated for $\text{X} = \text{Br}$ or I . For highly sterically-demanding phosphines such as $\text{P}(1\text{-Ad})(t\text{Bu})_2$ or $\text{P}(t\text{Bu})_3$, the OA products were not stable at the temperature required for the reaction and their decomposition generates the corresponding phosphonium salt $\text{L}\cdot\text{HX}$. The latter turned out to catalyze the OA.¹²⁰ This autocatalytic phenomenon can be limited for more accurate kinetic studies by adding a substoichiometric amount of hindered bases such as phosphazenes. For these phosphines as well as for QPhos (QPhos = pentaphenyl(di-tert-butylphosphino) ferrocene),¹²¹ kinetic studies clearly evidenced that different mechanistic paths operate depending on the nature of the halide. Indeed, aryl iodides react according to an associative pathway with the 14-electron $[\text{Pd}^0\text{L}_2]$. The OA was found to be first order with respect to ArI and zeroth order for the ligand, except for the case of PCy_3 for which the addition of an extra ligand inhibits the reaction rate through the formation of inactive $[\text{Pd}^0\text{L}_3]$, as observed by Baird.¹¹⁵ With aryl chlorides, the inverse first order dependency in added ligand implies the reversible formation of the monoligated $[\text{Pd}^0\text{L}]$, which is involved in the rate-limiting step. The complex $[\text{Pd}^{\text{II}}(\text{Ar})(\text{Cl})\text{L}]$ can result either directly from $[\text{Pd}^0\text{L}]$ or through the intermediate formation of the heteroleptic complex $[\text{Pd}^0\text{L}(\text{ArCl})]$. The OA with aryl bromides proceeds according to two competitive operative mechanisms with both $[\text{Pd}^0\text{L}]$ and $[\text{Pd}^0\text{L}_2]$ reacting. However, the main pathway involves the *bis*-ligated Pd complex (Scheme 9). It is worth noting that the kinetics of OA with hindered phosphines such as $\text{P}(t\text{Bu})_3$ strongly depends on the nature of the pre-catalyst.¹²²



Scheme 9. OA to monoligated $[\text{Pd}^0(\text{PCy}_3)]$ and *bis*-ligated $[\text{Pd}^0(\text{PCy}_3)_2]$ are competitive. Adapted from reference 115. Copyright 2009 American Chemical Society.

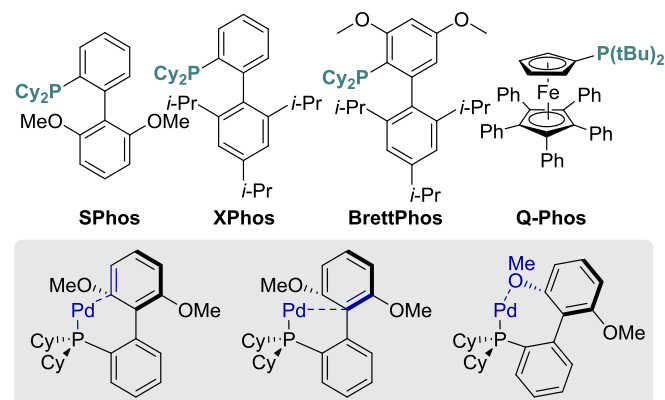
Similarly, OA of $[\text{Pd}^0(\text{P}(o\text{-Tol})_3)_2]$ to an aryl bromide proceeds at room temperature to form the corresponding *trans*-dimer of

$\text{Pd}(\text{II})$.^{123,124} On the basis of kinetic studies performed in various solvents, a dissociative pathway with $[\text{Pd}^0(\text{P}(o\text{-Tol})_3)]$ as the reactive intermediate was proposed (Scheme 10).



Scheme 10. Mechanism for the OA of ArBr to $[\text{Pd}^0(\text{P}(o\text{-Tol})_3)]$. Adapted with permission from reference 124. Copyright 1998 WILEY-VCH Verlag GmbH & Co.

In 1998, Buchwald and co-workers reported the use of ditertbutylbiarylphosphine to promote the amination of non-activated aryl halides such as aryl chlorides (Scheme 11).¹²⁵ This first report turned out to be the cornerstone of a new family of monodentate bulky and electron-rich ligands, among which SPhos (SPhos = 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl) and XPhos (XPhos = 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl), *t*Bu-XPhos, BrettPhos (BrettPhos = 2-(dicyclohexylphosphino)3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl), and *t*BuBrettPhos are very popular. The presence of *ortho* substituents on the second phenyl moiety prevents the catalyst depletion by preventing the formation of cyclopalladated species.



Scheme 11. Structure of some dialkylbiarylphosphines ligands. Adapted from reference 126. Copyright 2008 American Chemical Society.

These hindered dialkylbiarylphosphines proved to be efficient in amination,^{105,127,128} borylation,¹²⁹ formation of carbon-oxygen bonds¹³⁰ and cross-couplings.¹²⁶ These ligands allow the activation of a wide range of partners such as aryl chlorides, tosylates, and heteroaromatic halides and even nitro derivatives when using BrettPhos.^{131,132} They can be used either with $[\text{Pd}_2(\text{dba})_3]$ or $\text{Pd}(\text{II})$ pre-catalysts such as $[\text{Pd}^{\text{II}}(\text{OAc})_2]$, $[\text{Pd}^{\text{II}}\text{Cp}(\text{cinnamyl})]$, $[\text{Pd}^{\text{II}}(\text{cinnamyl})\text{Cl}]_2$ or palladacycles.^{106,133-135}

Based on molecular modelling performed at the DFT level, OA using Pd -ligated to Buchwald phosphines requires prior dissociation of $[\text{Pd}^0\text{L}_2]$ to $[\text{Pd}^0\text{L}]$.¹³⁶⁻¹³⁸ As calculated for PtBu_3 ,¹³⁹ this phosphine release step seems to be critical, with $23.5 \text{ kcal mol}^{-1}$ of energy barrier for SPhos. This dissociation is favored by the combination of both the steric hindrance of the ligand (cone angle estimated to be 256° for XPhos) and its electron-donating character. The resulting $[\text{Pd}^0\text{L}]$ complex can exist as several conformers, but one of them is stabilized via an η^1 interaction of metal center with the *ipso* carbon or the

heteroatom at the *ortho* position of the distal phenyl ring,¹⁹ or a η^2 -complexation with one of the double bond of this aromatic core.⁷⁸ The OA proceeds through a prior complexation of the aryl halide with the formation of $[\text{Pd}^0\text{L}(\text{ArX})]$ followed by the three-center insertion step to give the $[\text{Pd}^{\text{II}}(\text{Ar})(\text{L})\text{X}]$ complex, in which the halide is *trans* to the phosphorous atom. A related mechanism was verified for XPhos as a ligand.¹⁴⁰

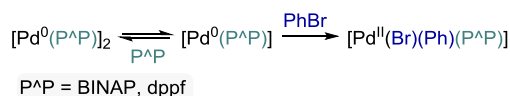
All these recent results on hindered monophosphine shed light on the possible involvement of the 12-electron $[\text{Pd}^0(\text{PPh}_3)]$ complex as the active catalyst in the oxidative addition.^{13,21,26,37}

Predictive tools have recently emerged to aid synthetic chemists in selecting the appropriate reaction catalyst. In this field, the Sigman group has developed a model using a multivariate correlation.¹⁴¹ However, this model has proven to be difficult to interpret. Nevertheless, by comparing the cone angle of various phosphines to that of PPh_3 , they concluded that smaller phosphines enhance Pd^0L_2 formation, while larger ones promote Pd^0L formation. This analysis supports the observed selectivity in the oxidative addition of aryl triflates, which react with Pd^0L_2 , as opposed to aryl chlorides, which react with Pd^0L .¹⁴¹ Sigman and Doyle then proposed to use a steric descriptor, the minimum percentage of buried volume, as a valuable tool to predict the reactivity of a Pd reaction as it allows to discriminate between mono and bis-ligated Pd(0).⁸⁵ More recently, Paci and Leitch have showcased the potential to predict the reactivity and selectivity of various (hetero)aryl electrophiles, including chlorides, bromides, and triflates, in oxidative addition. This prediction is based on the utilization of readily available molecular descriptors for the electrophile. First developed for PCy_3 -ligated Pd(0), they extended the predictive models to a wide array of trialkyl monophosphines.⁸⁴

5. Bidentate Phosphines

Bidentate phosphines are a popular choice for a variety of Pd-catalyzed reactions, such as Buchwald-Hartwig aminations and Tsuji-Trost allylations. Common catalytic systems encompass Pd(II) pre-catalysts, such as $[\text{Pd}^{\text{II}}\text{Cl}_2(\text{dppf})]$ and mixtures of bidentate phosphines with Pd(0) pre-catalysts (e.g. $\text{Pd}^0_2(\text{dba})_3$ or Pd(II) salts (e.g. $[\text{Pd}^{\text{II}}(\text{OAc})_2]$). First of all, based on molecular modelling performed at the DFT level using a simplified structural model, it has been evidenced that the steric decongestion of the metal active site originating from the ligand bite angle overcomes the awaited electronic effect, namely the raising in energy of the metal d orbitals.¹⁴² To further elucidate the influence of diphosphines on the oxidative addition to Pd, several representative systems have been studied in detail, unravelling a more complex and variegated mechanistic picture.

Hartwig and co-workers studied the reactivity of the tetracoordinated Pd(0) complexes $[\text{Pd}^0(\text{BINAP})_2]$ and $[\text{Pd}^0(\text{dppf})_2]$ in the context of Pd-catalyzed amination reactions.^{101,143,144} The kinetics of OA of PhBr to $[\text{Pd}^0(\text{BINAP})_2]$ at 40°C showed an order of -1 in added BINAP at low PhBr concentration and approached a saturation behavior with respect to PhBr, *i.e.* the rate of OA reached a maximum and did not increase at high PhBr-concentration. These data are consistent with the mechanism reported in Scheme 12: the coordinatively saturated, 18-electron complex $[\text{Pd}^0(\text{BINAP})_2]$ does not react with PhBr, but ligand dissociation generates the 14-electron complex $[\text{Pd}^0(\text{BINAP})]$, which is the active species.

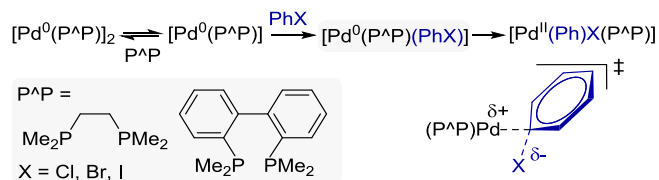


Scheme 12. OA of PhBr to BINAP- and dppf-ligated Pd(0). Adapted from reference 143. Copyright 1998 American Chemical Society.

In agreement with this mechanism, at PhBr saturation the reaction is solely controlled by the dissociation of BINAP and the observed rate is independent from the nature of the substituents on ArBr (Ar = Ph, 2-anisyl, 2-tolyl, 2,5-xylyl). The solvent polarity as well as the presence of inert salt (Bu_4NPF_6) or of primary amines did not significantly influence the reaction rate. The latter observation suggested that $[\text{Pd}^0(\text{BINAP})(\text{amine})]$ complexes do not play a role in OA,¹⁰³ which is relevant for the mechanism of Buchwald-Hartwig aminations.

The dppf-ligated complex $[\text{Pd}^0(\text{dppf})_2]$ behaved similarly to the BINAP analogue, but no saturation effect with respect to PhBr was noticed at high PhBr concentrations. The authors proposed that under these conditions one of the two dppf ligands could switch to a κ^1 coordination mode, thereby allowing PhBr to enter the coordination sphere to form a complex of formula $[\text{Pd}^0(\kappa^1\text{-dppf})(\kappa^2\text{-dppf})(\text{PhBr})]$ prior to OA.¹⁰¹ This behavior would be consistent with a reduced stabilization of dppf chelates compared to BINAP chelates, which is also supported by the formation of dppf-bridged dinuclear complexes $[(\kappa^2\text{-dppf})\text{Pd}^0(\mu\text{-dppf})\text{Pd}^0(\kappa^2\text{-dppf})]$.¹⁰¹ A small positive dependence of the reaction rate on ArI at very high concentration of ArI (up to 4 M) was also observed in the case of $[\text{Pd}^0(\text{BINAP})_2]$, but this effect was less preeminent in the case of ArBr and absent in the case of ArOTf.¹⁴⁵ This observation reinforces the hypothesis that $[\text{Pd}^0(\kappa^1\text{-BINAP})(\kappa^2\text{-BINAP})(\text{ArX})]$ could be a key intermediate formed before the OA step, since coordinating ability of ArX decreases in the order $\text{ArI} > \text{ArBr} \gg \text{ArOTf}$.

The formation of such pre-complexes was also highlighted in a theoretical study performed at the DFT level that examined the reaction of $[\text{Pd}^0(\text{P}^{\wedge}\text{P})_2]$ type model complexes ($\text{P}^{\wedge}\text{P} = \text{dmpe}, \text{BIMEP}$; $\text{dmpe} = 1,2\text{-bis}(\text{dimethylphosphino})\text{ethane}$, $\text{BIMEP} = 2,2'\text{-bis}(\text{dimethylphosphino-}1,1'\text{-biphenyl})$) (Scheme 13).¹⁴⁶ While dissociation of $\text{P}^{\wedge}\text{P}$ from $[\text{Pd}^0(\text{P}^{\wedge}\text{P})_2]$ is strongly endothermic, association of PhX with $[\text{Pd}^0(\text{P}^{\wedge}\text{P})]$ was computed thermodynamically favorable in all coordination modes: 1,2- η , 2,3- η and $\kappa\text{-X}$ for X = Cl, Br, I. η -Coordination is particularly favored, as PhX can act as a π -acceptor in this mode and stabilize the electron-rich d^{10} center, with the η^2 -binding mode leading directly to the transition state in which the C-X bond is cleaved. In this respect, a concerted transition state could be optimized for the molecules in the gas phase, but not in solution using COSMO as an implicit solvation model. However, taking solvation into account in the chemical model turned dissociation of X^- from $[\text{Pd}^0(\text{P}^{\wedge}\text{P})(\eta^2\text{-PhX})]$ kinetically accessible (almost thermoneutral and obviously entropically favorable). The resulting organo-Pd(II) complex *cis*- $[\text{Pd}^{\text{II}}(\text{Ar})\text{X}(\text{P}^{\wedge}\text{P})]$ could thus be formed by dissociation of X^- and subsequent barrierless association to $[\text{Pd}^{\text{II}}(\text{Ph})(\text{P}^{\wedge}\text{P})]^+$.¹⁴⁶

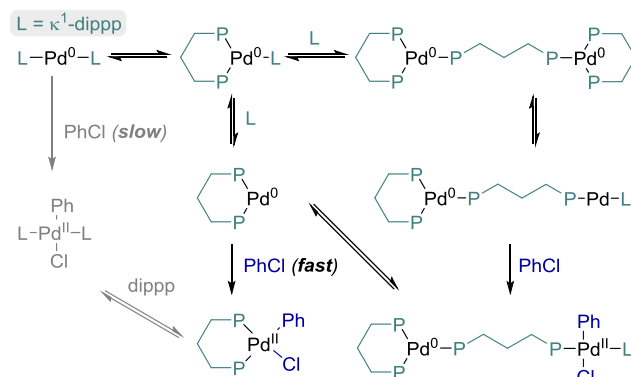


Scheme 13. OA of PhX (X = Cl, Br, I) to dmpe- and BIMEP-ligated Pd(0) complexes, as studied by DFT calculations. Adapted from reference 146. Copyright 2004 American Chemical Society.

The actual tendency of diphosphines to form chelate complexes can have a dramatic impact on the solution structure of Pd⁰ complexes and their reactivity towards OA. Chelation, which we already invoked above to explain the divergent behavior of dppf and BINAP, is even more relevant in the case of diphosphines having bulky alkyl groups. In this case, the balance between the chelate stabilization and the steric hindrance determines whether formation of chelates is favored or not. An elegant demonstration of the importance of these factors was provided by Milstein and co-workers, who studied a series of Pd(0) complexes of bidentate phosphines *i*Pr₂P-(CH₂)_n-P*i*Pr₂ (n = 2: dippe, n = 3: dippp, n = 4: dippb) and their reactivity with PhCl.^{147,148} Complex [Pd⁰(dippe)₂] (n = 2), coordinatively saturated with a distorted tetrahedral geometry, does not react with PhCl at 60°C. In this case, the 5-membered chelate ring is exceedingly stable and the complex is inert. The homologue [Pd⁰(dippp)₂] (n = 3) mainly exists as a coordinatively unsaturated, trigonal complex, better formulated as [Pd⁰(κ¹-dippp)(κ²-dippp)]. It reacts smoothly with PhCl at 60°C to give mainly *cis*-[Pd^{II}Cl(Ph)(dippp)]₂. The higher homologue [Pd⁰(dippp)₂] (n = 4) reacts with PhCl faster than the dippp complex, in virtue of its larger bite angle.^{149,150} For the same reason, it produces *trans*-[Pd^{II}Cl(Ph)(κ¹-dippp)₂] and oligomers instead of the *cis* κ²-complex.¹⁴⁷

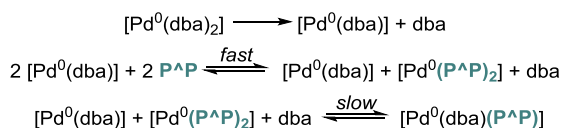
Complex [Pd⁰(dippp)₂] deserved special attention,¹⁴⁸ since it is an effective catalyst for carbonylation,¹⁵¹ reduction¹⁵² and formylation¹⁵³ of aryl chlorides, for which OA is the turnover-limiting step. As we mentioned, dippp has a poor chelate effect and it can serve as a bridging as well as a chelating ligand. The reaction of [Pd⁰(dippp)₂] with PhCl gives a mixture of *cis*-[Pd^{II}Cl(Ph)(κ²-dippp)] and *trans*-[Pd^{II}Cl(Ph)(κ²-dippp)], the former being both kinetically and thermodynamically favored. Kinetic data pointed out a complex mechanistic picture, which is depicted in its essential lines in Scheme 14. The major Pd⁰ species in solution is [Pd⁰(κ¹-dippp)(κ²-dippp)], which is in equilibrium with the active 14-electron species [Pd⁰(κ²-dippp)] by loss of dippp. The latter complex reacts in a fast reaction with PhCl to deliver *cis*-[Pd^{II}Cl(Ph)(κ²-dippp)]. An alternative pathway involves (unfavorable) isomerization of [Pd⁰(κ¹-dippp)(κ²-dippp)] to [Pd⁰(κ¹-dippp)₂], which can react with PhCl in a slow reaction yielding *trans*-[Pd^{II}Cl(Ph)(κ¹-dippp)₂]. This *trans* complex is in equilibrium with *cis*-[Pd^{II}Cl(Ph)(κ²-dippp)] via loss of dippp. Other pathways involving dinuclear or polynuclear dippp-bridged Pd(0) complexes (not shown in Scheme 14) are also conceivable.¹⁴⁷

The rates of reaction of substituted chlorobenzenes with [Pd⁰(dippp)₂] showed a poor correlation with Hammett's σ constants, but an excellent one with the σ⁻ parameter through a high ρ = +5.2 constant (to be compared with ρ = 2 observed for Pd⁰/PPh₃ complexes, see section 2.1).²⁴ This indicates a S_NAr-type character of the OA process with the strongly basic and nucleophilic [Pd⁰(dippp)] complex.¹⁴⁸



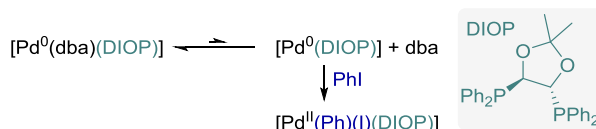
Scheme 14. OA of PhCl to dippp-ligated Pd(0) complexes. *i*Pr groups on P atoms are omitted for clarity. Adapted from reference 147. Copyright 1993 American Chemical Society.

Up to now, we have discussed the reactivity of homoleptic diphosphine-ligated complexes. However, mixture of heteroleptic complexes are often used in practical applications, resulting from Pd pre-catalysts and bidentate phosphines mixture. Amatore and Jutand analyzed in depth the behavior of [Pd⁰(dba)₃]/diphosphine mixtures toward oxidative addition, which is a popular system for catalytic reactions (Scheme 15).⁹³ Mixtures of [Pd₂(dba)₃] with 2 equiv. of P^AP generally gave [Pd⁰(P^AP)₂], which is practically inert towards PhI at room temperature (P^AP = dppm, dppe, dppp, dppb, dppf, DIOP; dppm = bis(diphenylphosphino) methane, dppe = 1,2-bis(diphenyl phosphino)ethane, dppp = 1,3-bis(diphenylphosphino)propane, dppb = 1,4-bis(diphenylphosphino)butane, see Scheme 16 for the structure of DIOP). For instance, treatment of [Pd₂(dba)₃] with DIOP (2 equiv) quickly lead to [Pd⁰(DIOP)₂], which gave no reaction with PhI (1000 equiv) at room temperature for 2 h. When Pd(dba)₂ and DIOP were mixed in 1:1 molar ratio, [Pd⁰(DIOP)₂] was formed first, but on longer reaction times ligand redistribution gave [Pd⁰(dba)(DIOP)]. Other ligands (dppm, dppe, dppp, dppb, dppf) behave similarly, but BINAP displaced slowly dba forming only [Pd⁰(dba)(BINAP)]. [Pd⁰(BINAP)₂] could not be observed even after standing overnight at 40°C with excess BINAP.



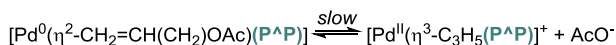
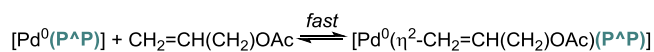
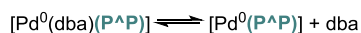
Scheme 15. OA to [Pd₂(dba)₃]/diphosphine mixtures (P^AP = dppm, dppe, dppp, dppb and dppf). Adapted from reference 93. Copyright 1997 American Chemical Society.

The complex [Pd⁰(dppf)₂] behaves similarly to the BINAP analogue. Kinetic data collected for DIOP highlighted that the reaction with PhI takes place by a dissociative mechanism in which the active species is again the 14-electron [Pd⁰(P^AP)] complex formed by loss of dba (Scheme 16). [Pd⁰(dba)(DIOP)] was shown to be at least 600 times less reactive than [Pd⁰(DIOP)], but significantly more abundant in the reaction mixture. Similar conclusions hold for P^AP = BINAP.⁹³



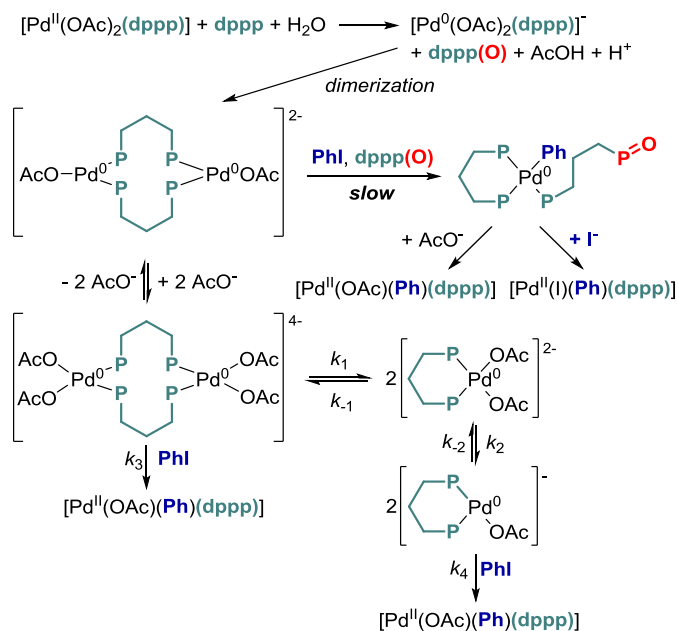
Scheme 16. OA of PhI with $[\text{Pd}^0(\text{dba})(\text{DIOP})]$. Adapted from reference 93. Copyright 1997 American Chemical Society.

The reaction of 1:1 mixtures of $[\text{Pd}_2^0(\text{dba})_3]$ and dppb or dppf with allyl acetate in DMF was similarly studied.¹⁵⁴ Three main characteristic features distinguish this transformation from the analogous reactions involving aryl halides: (i) cationic $[\text{Pd}^0(\eta^3\text{-C}_3\text{H}_5)(\text{P}^{\wedge}\text{P})]^+$ with AcO^- as counter-anion is formed; (ii) the OA is reversible; (iii) allyl acetate first displaces dba from $[\text{Pd}^0(\text{dba})(\text{P}^{\wedge}\text{P})]$ giving a neutral η^2 -complex $[\text{Pd}^0(\eta^2\text{-CH}_2=\text{CHCH}_2\text{OAc})(\text{P}^{\wedge}\text{P})]$, which then reacts in a unimolecular step to deliver the above-mentioned cationic Pd(II) complex and AcO^- (Scheme 17).¹⁵⁴ DIOP behaves differently from dppb and dppf since the OA product $[\text{Pd}^{\text{II}}(\eta^3\text{-C}_3\text{H}_5)(\text{DIOP})]^+$ does not form directly from $[\text{Pd}^0(\eta^2\text{-CH}_2=\text{CHCH}_2\text{OAc})(\kappa^2\text{-DIOP})]$. Indeed, the intervention of an additional molecule of allyl acetate is necessary to yield the active intermediate $[\text{Pd}^0(\eta^2\text{-CH}_2=\text{CHCH}_2\text{OAc})_2(\kappa^1\text{-DIOP})]$.¹⁵⁵



Scheme 17. OA of allyl acetate to diphosphine-ligated Pd(0). $\text{P}^{\wedge}\text{P}$ = dppb, dppf. Adapted with permission from reference 154. Copyright 2001 WILEY-VCH Verlag GmbH & Co.

Other electron-poor olefins that could behave similarly to dba may be present in catalytic reactions and influence the reactivity of Pd(0) complexes. Methyl acrylate (MA) is a typical substrate in Heck reactions. Jutand and Brown studied the OA of ArI and ArOTf to isolated $[\text{Pd}^0(\text{dppf})(\text{MA})]$.⁹¹ Surprisingly, methyl acrylate has no inhibitory effect on these reactions, thus ruling out a dissociative mechanism, *i.e.* it is not necessary that methyl acrylate decoordinates to form $[\text{Pd}^0(\text{dppf})]$ for the oxidative reaction to take place. However, the reaction is accelerated by the presence of $\text{Eu}(\text{OTf})_3$ that most likely traps methyl acrylate and promotes the formation of $[\text{Pd}^0(\text{dppf})]$ that is more reactive than $[\text{Pd}^0(\text{dppf})(\text{MA})]$. Interestingly, PhI reacts with $[\text{Pd}^0(\text{dppf})(\text{MA})]$ approximately 4300 times slower than it does with $[\text{Pd}^0(\text{PPh}_3)_4]$, while this ratio is approximately of 5 in the case of PhOTf.⁹¹

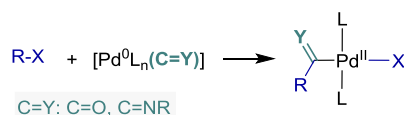


Scheme 18. Mechanism for the OA of PhI to the Pd(0) complex generated from $[\text{Pd}^{\text{II}}(\text{OAc})_2]$ and 2 equiv. of dppp in the presence of AcO^- . For clarity, Ph rings are omitted from the ligand. Adapted from reference 91. Copyright 1999 American Chemical Society.

Pd(II) pre-catalysts are often used in catalysis together with diphosphine ligands. In this case, the ligand $\text{P}^{\wedge}\text{P}$ can act as a reducing agent, being thus oxidized to the mono-oxide $\text{P}^{\wedge}\text{PO}$, which complicates the mechanistic picture. The case of $[\text{Pd}^{\text{II}}(\text{OAc})_2]$ with dppp was studied in details by Amatore and Jutand.¹⁵⁶ The oxidation of dppp by $[\text{Pd}^{\text{II}}(\text{OAc})_2]$ is reversible in the absence of water. A stable Pd(0) complex is quantitatively formed with 2 equiv. of dppp, water, and a base (NEt_3 , to capture H^+). The OA of PhI gives a cationic complex, $[\text{Pd}^{\text{II}}(\text{Ph})(\text{dppp})(\text{dpppO})]^+$, in which dpppO acts as a monodentate ligand. $[\text{Pd}^{\text{II}}(\text{Ph})(\text{OAc})(\text{dppp})]$ is formed in the presence of added AcO^- . This transformation relies on a complex reaction network whose kinetics was investigated in the presence of added AcO^- (Scheme 18). It involves reactive dimeric or/and monomeric Pd(0) complexes ligated by AcO^- , whose relative reactivity depends on PhI concentration.¹⁵⁶ In this context, it is also important to mention that the diphosphine mono-oxide ligands formed by oxidation of diphosphines by Pd(II) pre-catalysts may serve as ligands for species that are active in catalytic cycles, such as XantPhosO in C-H activations,¹⁵⁷ dppfO in Suzuki couplings,¹⁵⁸ and chiral diphosphines in asymmetric transformations.¹⁵⁹

6. Carbene-Type Ligands

Carbon monoxide (CO), isocyanide (RNC) and *N*-heterocyclic carbenes (NHCs) are isoelectronic moieties sharing a common carbenic character. As such, they are ambivalent ligands, being both π -acceptors and σ -donors,^{160,161} and reagents being both nucleophilic and electrophilic. The σ -donation reinforces the electronic density at the Pd(0) center making OA easier – at the cost of more difficult RE. On the contrary, Pd(0) featuring π -acidic ligands are less active toward OA while offering lower energy barrier for RE.¹⁶²⁻¹⁶⁴ They can also act as substrates by inserting in the C-Pd bond formed after OA (Scheme 19).



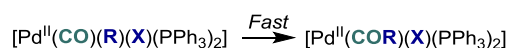
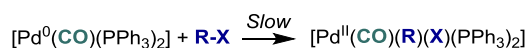
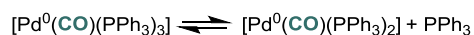
Scheme 19. OA of aryl and alkyl halides (RX) to $[Pd^0(C=Y)(PPh_3)_3]$ and subsequent migration of the carbene-type ligand (C=Y).

6.1. OA to Carbonyl-Pd(o) Complexes

Carbonylative (or decarbonylative) steps are conveniently associated to OA in synthesis to interconvert halide and pseudo-halide derivatives and carboxyl derivatives.¹⁶⁵⁻¹⁶⁸ Over the years, alternative methods that replace toxic carbon monoxide by easier-to-handle CO surrogates have been developed.¹⁶⁹ Surprisingly only few researchers have explored the mechanism for the OA of alkyl and aryl halides into carbonyl Pd(0) complexes. The main outcome is that while CO coordination is required for the insertion to proceed, it also inhibits OA. For instance, Castanet and collaborators reported¹⁷⁰ that a finely adjusted CO pressure is crucial in Pd(0)-catalyzed carbonylation of benzyl chlorides. Working at relatively low CO pressure favors OA by avoiding the formation of insoluble and electron-poor carbonyl complexes such as $[Pd^0(CO)(PPh_3)_3]$ and the trinuclear $[Pd^0_3(CO)_3(PPh_3)_4]$ complex. This condition-dependency was also reported by other groups.^{171,172}

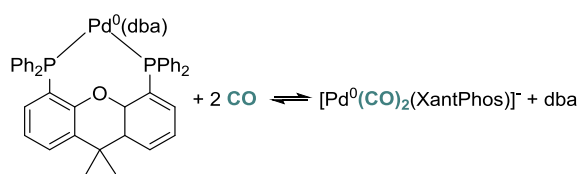
Several studies tackled the structure and the reactivity of carbonyl-ligated Pd(0) complexes towards OA. After the characterization of both mono- and tri-metallic mixed carbonyl-phosphine complexes,¹⁷³⁻¹⁷⁵ the group of Uchida further studied their reactivity in OA. Their initial focus was on complex $[Pd^0(CO)(PPh_3)_3]$ and its straightforward transformation into $Pd^0(PPh_3)_4$ in the presence of excess phosphine.^{174,176} To complement, the stoichiometric OA of various alkyl and aryl halides onto square-planar carbonyl complex $[Pd^0(CO)(PPh_3)_3]$ under a CO atmosphere has been investigated.¹⁷⁷ In this case, products of OA could not be observed because the subsequent insertion of CO occurs more rapidly than OA (Scheme 20).

Interestingly, trinuclear Pd carbonyl complexes such as $[Pd^0_3(CO)_3(PPh_3)_4]$, $[Pd^0_3(CO)_3(PPh_3)_3]$ display a different behavior. While they are not soluble in apolar solvents, they efficiently catalyze the carboalkoxylation of iodobenzene in methanol with an overall catalytic performance higher than those characterized by monomeric $[Pd^0(CO)(PPh_3)_3]$ or $[Pd^{II}Cl_2(PPh_3)_2]$ complexes.¹⁷⁸ To the best of our knowledge, no further study has been reported on these polymetallic species, as well as on their possible involvement in reactions.

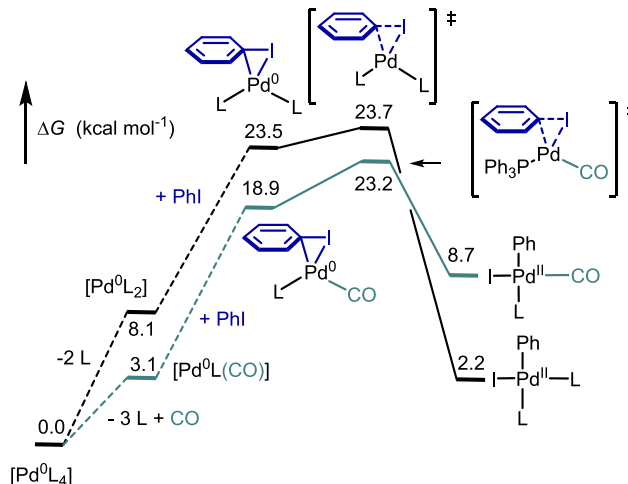


Scheme 20. Mechanism for OA followed by 1,1 insertion.¹⁷⁷ R = vinyl, allyl and $CH_2CMe=CH_2$, X = Cl; or R = Bn, X = Br; or R = Me, Ph, X = I.

Among the Pd-CO family of complexes, Grushin and Macgregor reported in 2014 a joint theory and experimental mechanistic investigation¹⁷⁹ on the Pd-catalyzed azidocarbonylation of aryl iodides. In this case, under CO atmosphere, dba ligand of the $[Pd^0(dba)(XantPhos)]$ complex is displaced by two CO molecules to yield the electron-poor dicarbonyl complex $[Pd^0(CO)_2(XantPhos)]$ (Scheme 21).



Scheme 21. Competition between CO and dba coordination on $[Pd^0(XantPhos)]$. Adapted from reference 179. Copyright 2014 American Chemical Society.

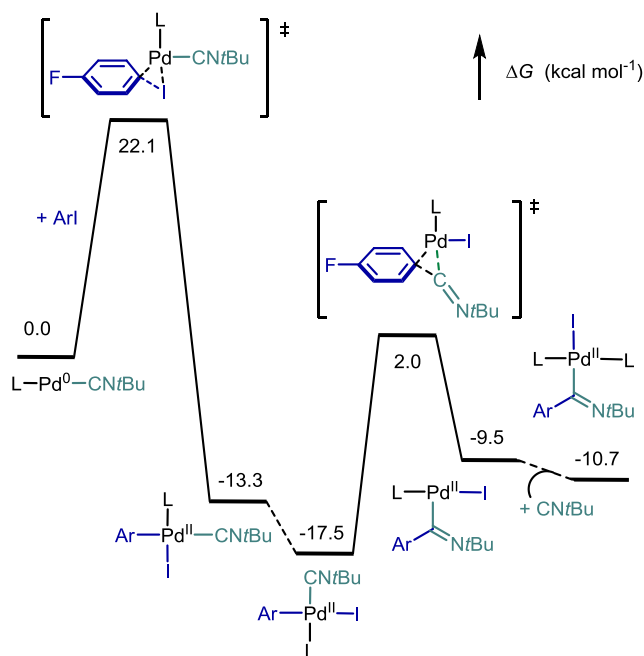


Scheme 22. Gibbs energy profile of the CO concentration-dependent mechanisms of the OA of PhI to Pd^0L_4 , L = PPh_3 .¹⁷⁹ Free energies are given in kcal mol⁻¹. Adapted with permission from reference 176. Copyright 2017 Royal Society of Chemistry.

Though these complexes are active toward the OA of Ar-I – $[Pd^0(dba)(XantPhos)]$ being slightly faster, the equilibrium between both can be adapted by adjusting CO pressure. Based on calculations performed at the DFT level, two different pathways, depending on the CO concentration, were reported for the OA of ArI. At low CO pressure, carbonyl-free complex promotes a fast OA prior to CO coordination while at high pressure, CO coordination occurs before OA, leading to a less active electron-deficient phosphine-carbonyl complex. To complement, Kégl and co-workers recently reported the speciation of $Pd^0(PPh_3)_4$ under carbonylative conditions by means of DFT calculations.¹⁷⁶ Among monometallic species, $[Pd^0(PPh_3)(CO)_3]$, $[Pd^0(PPh_3)(CO)_2]$ and $[Pd^0(PPh_3)(CO)]$ are likely in equilibria, whereas $[Pd^0(PPh_3)(CO)_3]$ is the most stable complex, and the formation of monoligated Pd^0L (L = PPh_3 , CO) complexes is not possible. The OA of PhI to $[Pd^0(PPh_3)(CO)]$ was computed slightly faster than to $[Pd^0(PPh_3)_2]$ (Scheme 22).

6.2. OA to Pd(o)-Isocyanide Complexes

Isocyanides may be used as reagents in Pd-catalyzed cross-coupling reactions, usually to exploit the ability of RNC to insert into the Pd-C bond after OA.¹⁸⁰⁻¹⁸² However, OA of aryl halides to isocyanide-ligated Pd(0) has not been intensively investigated. Details concerning the mechanism remain as scattered as for carbon monoxide, while isocyanides can also act as ligands and substrates.¹⁸³



Scheme 23. Gibbs energy (kcal mol^{-1}) profile calculated for the Pd(0) OA into the C-I bond of $p\text{FC}_6\text{H}_4\text{I}$ and the subsequent isocyanide insertion. Adapted with permission from reference 184. Copyright 2016 WILEY-VCH Verlag GmbH & Co.

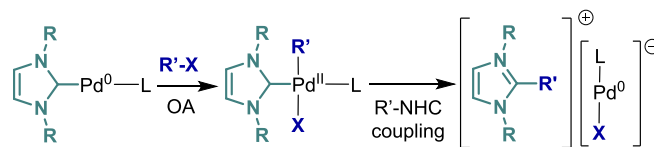
In 2016, Perego, Ciofini and Grimaud investigated the OA of 4-fluoriodobenzene to $\text{Pd}^0(\text{dba})_2$ in the presence of $t\text{BuNC}$.¹⁸⁴ Based on DFT calculations (Scheme 23), substitutions of dba with $t\text{BuNC}$ lead to the formation of $[\text{Pd}^0(t\text{BuNC})_2]$ as the major species. ^{19}F NMR-monitoring revealed a rapid OA with a second-order kinetics $r = k[\text{Pd}^0][\text{ArI}]$. Interestingly, OA is zeroth-order with respect to $t\text{BuNC}$, that is indicative of an associative pathway, *i.e.* no isocyanide decoordination is required for OA. This was confirmed by molecular modelling performed at the DFT level. The overall Gibbs energy barrier for OA was calculated to $22.1 \text{ kcal mol}^{-1}$.

In the context of the Suzuki-Miyaura coupling, Figueroa and co-workers reported in 2017 the reactivity of Pd-isocyanide complexes towards aryl halides.¹⁸⁵ Indeed, the cross-coupling of aryl bromides with boronic acids performs well using catalytic amount of $[\text{Pd}^0(\text{CN-Y})_2]$ ($\text{Y} = 2,6\text{-}(\text{iPr})_2\text{C}_6\text{H}_3_2\text{C}_6\text{H}_3$) in $i\text{PrOH}$, under basic conditions at room temperature. Under these conditions aryl chlorides do not react. A dissociative pathway involving monoligated $\text{Pd}^0(\text{CN-Y})$ for the OA of aryl bromides has been suggested based on the decrease of the reaction rate in the presence of an excess of isocyanide. The easy formation of the electron-rich monoligated $[\text{Pd}^0(\text{CNAr})]$ and its enhanced reactivity was rationalized by a strong π -backbonding between the Pd d_{xy}/d_{yz} orbitals and the isocyanide π^* orbitals, as revealed by calculations performed at the DFT level.

6.3. OA to Pd(o)-NHC Complexes

Since their first use by Herrmann in 1995,¹⁸⁶ *N*-Heterocyclic Carbenes (NHC) ligands have been widely used in synthesis, and nowadays they are suitable ligands for Pd-catalyzed amination, Negishi, Suzuki-Miyaura and Heck cross-coupling reactions.^{186,187} NHCs are strong σ -donors,^{188,189} and weak π -acceptors, and have electronic properties that enable the activation of strong bonds such as C-Cl.¹⁹⁰ Moreover, the

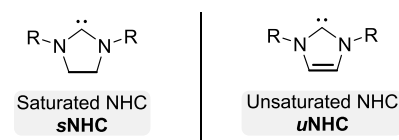
stability of the Pd-NHC complexes, as well as their reactivity in cross-couplings can be efficiently tuned by using *i.* saturated (imidazoline) or unsaturated (imidazolidine) scaffolds, and *ii.* judiciously chosen substituents at nitrogen atoms.¹⁹¹⁻¹⁹³ However, Pd(NHC) complexes may be prone to reductive elimination forming $\text{R}'\text{-NHC}$ (Scheme 24) that is often detrimental for the reaction yields,¹⁹⁴ it has been reported that this Pd-NHC bond cleavage is sometimes beneficial because it forms catalytically active NHC-free Pd complexes or clusters. This specific topic has been recently reviewed by Ananikov and co-workers.¹⁹⁵



Scheme 24. OA of $\text{R}'\text{-X}$ to $[\text{Pd}^0\text{L}_2]$ L = NHC and subsequent $\text{R}'\text{-NHC}$ coupling. Adapted with permission from reference 194. Copyright 1995 Elsevier Science S.A.

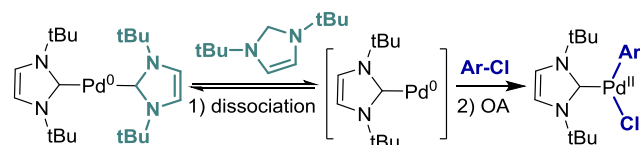
6.3.1 Unaturated vs Saturated NHC-Pd complexes

Depending on the nature of the carbene ligand, unsaturated NHC ($u\text{NHC}$) with an imidazolium or saturated NHC ($s\text{NHC}$) with an imidazolium backbone (Scheme 25), $[\text{Pd}^0(\text{NHC})_2]$ complexes behave differently toward OA.



Scheme 25. General structures of saturated and unsaturated NHC ligands.

In 2000, the group of Herrman described the synthesis of various $[\text{Pd}^0(u\text{NHC})_2]$ complexes (with R = Mes, $t\text{Bu}$, $i\text{Pr}$ or Cy substituents at nitrogen atoms) starting from $[\text{Pd}^0(\text{P}(o\text{-Tol})_3)_2]$ and their relative activity in the Suzuki-Miyaura cross-coupling.¹⁹⁶ The first stoichiometric OA to a Pd(0) with $u\text{NHC}$ ligands was described in 2002.¹⁹⁷ In 2003, Leonard experimentally demonstrated that, starting from $[\text{Pd}^0(u\text{NHC})_2]$, OA takes place to $[\text{Pd}^0(u\text{NHC})]$ following a dissociative scheme (Scheme 26).¹⁹⁸ This is in good agreement with later theoretical investigations of Lonsdale on the OA of chlorobenzene and chloromethane to $[\text{Pd}^0(\text{cyclo-C}(\text{NRCH})_2)_2]$ catalyst¹⁹⁰ and with the early observation by Grasa that the addition of an excess of NHC ligand slows the reaction kinetics down.¹⁹⁹ OA was found to be sensitive to the presence of EWGs and EDGs at the *para* position of ArCl , which respectively accelerates and decelerates the process.¹⁹⁸

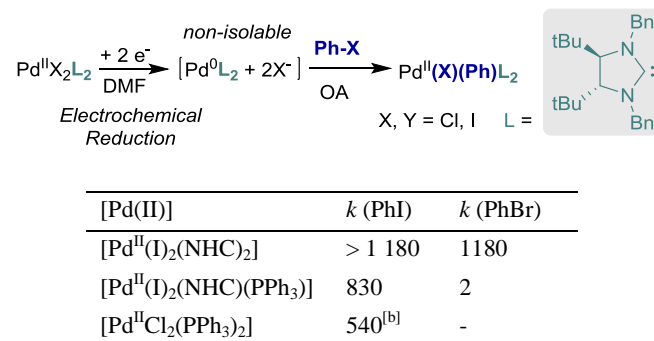


Scheme 26. Dissociative pathway for OA of aryl chlorides at Pd complexes bearing unsaturated NHC ligands.

In 2018, Ananikov investigated the influence of substituents for the OA of $\text{R}'\text{-X}$ to mixed unsaturated R-NHC-pyridine Pd(0) complexes using DFT calculations.²⁰⁰ The ease at which $\text{R}'\text{-X}$ undergoes OA to Pd(0) depends on the nature of R, R' and X.

Complexes bearing saturated NHCs (*s*NHCs) tend to be more reactive than *u*NHC-ligated ones,¹⁹² the first [Pd⁰(*s*NHC)₂] complex was isolated in 2001 by Wilson and McKercher.²⁰¹ Jutand explored the reactivity of *in-situ* electrogenerated Pd(0) complexes bearing *s*NHCs towards OA.²⁰² The reaction rates for OA with PhBr were estimated by Cyclic Voltammetry (Table 3).

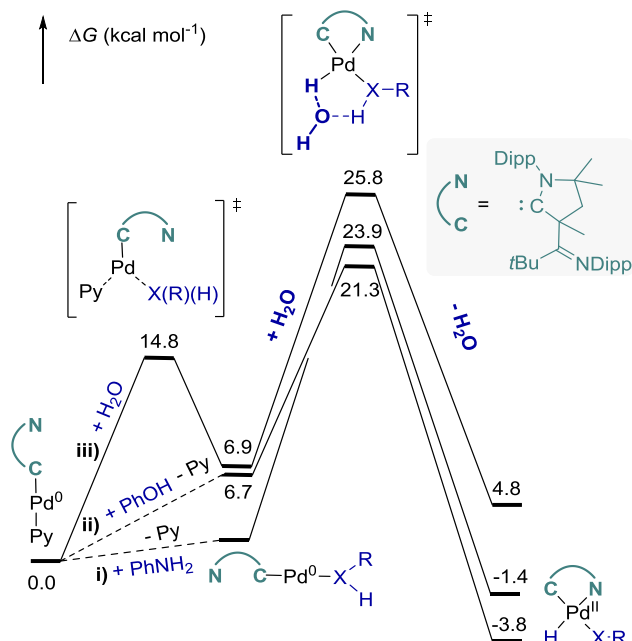
Table 3. Reaction rates (M⁻¹ s⁻¹) estimated for the OA of PhX (X = I, Br) at *in-situ* electro-chemically generated Pd(0) complexes in DMF. Reproduced with permission from references 202 and 27. Copyright 1999 and 2003 Elsevier Science S.A.



^[a]V vs SCE; ^[b]In THF instead of DMF.²⁷

Since *s*NHCs are stronger σ -donor than PPh₃ OA rate decreases as the two *s*NHC ligands are successively replaced by PPh₃. Conversely, OA of aryl halides was found to proceed through an associative mechanism with Pd⁰ species bearing *s*NHC ligands, *i.e.* with no preliminary NHC dissociation and [Pd⁰(*s*NHC)₂] being the active intermediate.¹⁹¹ To the best of our knowledge, the exact origin of this switch in mechanism has not been fully elucidated. In particular, the frontier between electronic effects and steric hindrance is rather ambiguous, and should be further investigated.

Exploring variation along the NHC series, the group of Bertrand recently reported the synthesis of Pd(0)-CAAC complexes (CAAC = cyclo(alkyl)(amino)carbene) and its use for the activation of inert bonds.²⁰³⁻²⁰⁷ The insertion of Pd(0) bearing cyclic (alkyl)(amino)carbene ligand into X-H bonds (with X = O or N) has been explored by combining ¹H-NMR and theoretical calculations at the DFT level (Scheme 27).²⁰⁸ The kinetics of the OA of water to Pd(0) follow a second order with respect to water, which indicates that two water molecules are involved in the OA reaction. Using [Pd⁰(CAAC)(Py)] as a pre-catalyst, the reaction starts with the concerted substitution of pyridine with the substrate (RXH = H₂O, PhOH or aniline) to give [Pd⁰(CAAC)(RXH)] intermediate, which then undergoes OA. OA occurs in a concerted way through a water-assisted-5-membered-ring transition state.



Scheme 27. Gibbs energy profile for the OA of water, phenol and aniline (RXH with RX = OH, PhO and PhNH, dark blue) to [Pd⁰(CAAC)(Py)] complex in THF. Energies are given in kcal mol⁻¹. Adapted with permission from reference 208. Copyright 2020 WILEY-VCH Verlag GmbH & Co.

6.3.2 R'-NHC Coupling: Deactivation or Activation path?

In the family of NHC-ligated system, the steric hindrance of the R substituents at the N atoms has a strong influence on the stability of the free NHC ligands²⁰⁹ and their associated Pd-complexes.²¹⁰ Pd-NHC bond cleavage is usually considered as a detrimental side-reaction^{194,211} and can be sometimes avoided by employing hindered, electron-rich substituents at nitrogen.²¹⁰ However, in 2017 Ananikov reported that R'-NHC coupling can benefit Mizorecki-Heck reaction at low catalyst concentration, due to the high activity of the naked Pd(0) species formed. Such mechanisms in which Pd(0) is not bound to NHC anymore were tagged as "NHC-disconnected mechanisms".²¹² In 2019, based on experiment (NMR, MS, X-ray characterization) and molecular modelling at the DFT level, they further evidenced the formation of the ion pair [PdX]⁻ / R'-NHC⁺ (R' = H or Ar, X = Cl, I or Br) (Scheme 22) (see section 3.1 for the detailed discussion about anionic Pd(0) effect) in the catalytic cycle of the Pd-NHC catalyzed Mizoroki-Heck coupling of aryl iodides with acrylates.²¹³ Comparison of DFT computed pathways for ionic and neutral pathways indicates that energy barrier for OA at ionic complex [Pd⁰(I)(PhI)] is about twice that of direct OA at the neutral [Pd⁰(NHC)] complex ($\Delta G^\ddagger = 9.3$ vs 4.7 kcal mol⁻¹, $\Delta H^\ddagger = 8.9$ vs 4.7 kcal mol⁻¹), but the reverse trend is then observed for β -H elimination. Theoretical investigations of OA at NHC-disconnected systems – in which the formation of Pd nanoparticles can be envisaged – may suffer from the limitations of commonly used static DFT approach (*i.e.* nanoparticle speciation, active-site identification, dynamic behavior, solvent effects). The exploration of such systems should greatly benefit from *ab initio* molecular dynamic approaches.^{214, 215} This approach was recently used by the group of Ananikov to elucidate the R-NHC coupling mechanism with in a solvent cage.²¹⁶ Experimentally, the dynamic structure of Pd complex-

es and/or particles in solution can be potentially explored by Extended X-ray Absorption Fine Spectroscopy (EXAFS) complemented by simulated EXAFS spectra from molecular dynamics simulations.²¹⁷⁻²¹⁹

7. OA to Polynuclear Pd Species

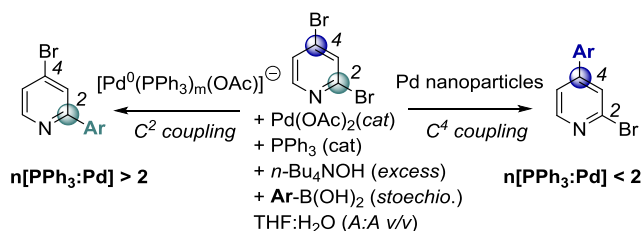
Several recent reports have evidenced the role played by Pd dimers and trimers in catalytic reactions, therefore a deeper understanding of such polynuclear Pd systems is crucial to efficiently tune the concentration of active species. While reviews written by Mingos, Kurosawa, Zhao, and Schoenebeck discuss in detail the structures and reactivity trends of Pd clusters,²²⁰⁻²²³ we focus in this section on the experimental conditions that lead to the formation of Pd clusters and the mechanism of OA reactions involving these species.

7.1 Formation & Activity of Polynuclear Pd Complexes

Amatore and Jutand reported that Pd(0) electrogenerated from $[\text{Pd}^{\text{II}}\text{Cl}_2(\text{PPh}_3)_2]$ in the absence of added phosphine consists in a mixture of a mono- and di-nuclear Pd(0) complexes (see also section 3.1). A second order in Pd(0) was reported for the OA of PhI to electrogenerated Pd(0), indicating that a dimer should be involved in the OA of PhI to Pd(0).⁶⁷ This is to our knowledge the first hints about a possible cooperative effects between two Pd(0) centers for OA.

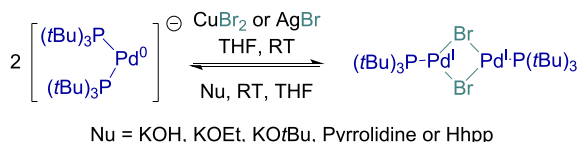
It has been reported several times that a 1:1 mixture of Pd(0):phosphine leads to optimal yields for cross-coupling reactions, especially for the Buchwald-Hartwig amination.^{199,224-227} Ozawa and co-workers, followed by Amatore and Jutand, explored the reduction of Pd(II) in the presence of bidentate phosphines.^{156,228} At least 2 equivalents of dppp are necessary to reduce $[\text{Pd}^{\text{II}}(\text{OAc})_2]$ into Pd(0) while a biphosphine mono-oxide is released during the process (see section 5). Kinetic experiments suggest that OA of PhI may occur via two parallel pathways respectively involving monomeric and dimeric Pd(0) complexes.¹⁵⁵

More recently, Fairlamb highlighted the critical effect of the phosphine-to-Pd ratio to determine whether Pd monomers or clusters are formed.³ Using 2,4-dibromopyridines as substrates, they evidenced a remarkable switch from C2 to C4 selectivity tuned by the $\text{PPh}_3:\text{Pd}$ ratio (n) (Scheme 28). When $n \geq 2$, the expected C² regioselectivity is observed, likely promoted by $[\text{Pd}^0(\text{PPh}_3)_m(\text{OAc})]$. Interestingly, a stable dinuclear Pd(I) complex $[\text{Pd}^{\text{I}}_2(\mu\text{-OAc})(\mu\text{-PPh}_2)(\text{PPh}_3)_2]$ was earlier characterized by X-ray diffraction and ¹H-NMR spectroscopies for $n = 2$.² When $n \leq 2$, the C⁴ coupling product is observed. This switch in selectivity is attributed to the formation of Pd(0) nanoparticles, detected by Transmission Electron Microscopy.²²⁹ Moreover, a beneficial effect of quaternary ammonium salts on C4 selectivity was reported. All together these observations confirm that tuning Pd aggregation state is key to control the OA selectivity. In line with these mechanistic investigations, Neufeldt recently reported an unusual C4 selectivity for 2,4-dichloropyridines obtained under ligand-free Jeffery conditions.²³⁰ Interestingly, a switch in selectivity toward C2-coupling is obtained when using NHC ligands.²⁵¹ Based on calculations at a DFT level, the authors showed this switch in selectivity is caused by the formation of monomeric 12-electrons species (PdL).



Scheme 28. Investigations by Fairlamb and co-workers on the $[\text{Pd}^{\text{II}}(\text{OAc})_2]/\text{PPh}_3$ speciation in the presence of various ratio n ($\text{PPh}_3:[\text{Pd}^{\text{II}}(\text{OAc})_2]$). Adapted from reference 3. Copyright 2021 American Chemical Society.

Schoenebeck²³² demonstrated the crucial role of additives to tune the formation of $[\text{Pd}^{\text{I}}(\text{PrBu}_3)]_2$ dimer. Pd(I) dimer can be formed *via* oxidation of $[\text{Pd}^0(\text{PrBu}_3)_2]$ by $[\text{Ag}^{\text{I}}\text{Br}]$ or $[\text{Cu}^{\text{II}}\text{Br}_2]$ salts,²³³ while addition of a nucleophile can regenerate Pd(0) (Scheme 29).²³² Such additives are commonly encountered in Sonogashira or Suzuki-Miyaura cross-couplings so that they can likely influence the catalyst activity.²³²



Nu = KOH, KOEt, KO^tBu, Pyrrolidine or Hhpp

Scheme 29. Influence of additives (salt and nucleophiles) on the formation and dissociation of Pd(I)-dimers. Hhpp = 1,3,4,6,7,8-hexahydro-2H-pyrimido[1,2-a]pyrimidine. Adapted from reference 232. Copyright 2015 American Chemical Society.

All in all, it is clear that the *in-situ* formation of polynuclear Pd species should not be underestimated, and should even be systematically questioned in any mechanistic investigations. Elucidating the key factors (solvent effects, role of ancillary ligands, salt effects, ...) that control – under conditions that are relevant to catalysis – the aggregation of monomeric Pd to form polynuclear species should enable controlling the nuclearity, and consequently tuning the reactivity of such species in solution (number of active species, ...). Trends may be deduced from joined experimental (EXAFs, MET, ...) and theoretical static and dynamic approaches.

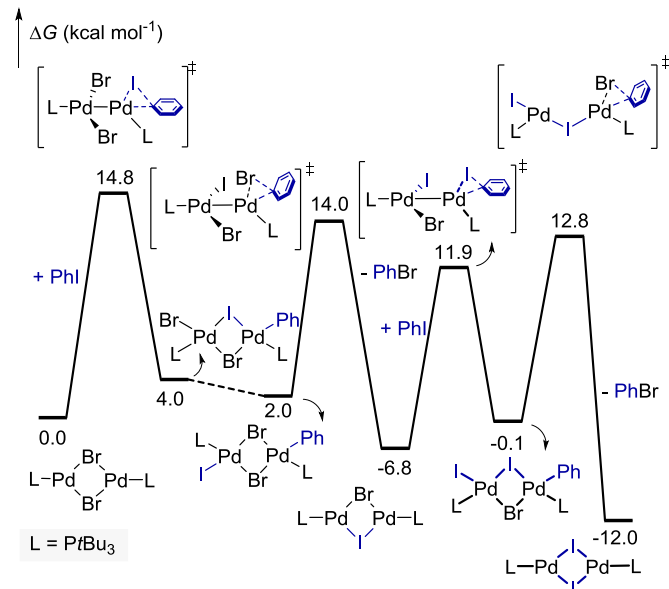
7.2 OA to Pd(I) and Pd(o) Dimers and Trimers

The reactivity of dinuclear $[\text{Pd}^{\text{I}}\text{Br}(\text{PrBu}_3)]_2$ in amination reactions has been explored by Hartwig and co-workers.²²⁷ It was suggested that this dimer acts as a reservoir of 12-electron $[\text{Pd}^0(\text{PrBu}_3)]$ intermediate. In a series of publications, the group of Vilar studied the synthesis,²³⁴ characterization and reactivity of dinuclear $[\text{Pd}^{\text{I}}\text{X}(\text{PrBu}_3)]_2$ complexes (X = Br or I).^{234,235} Vilar, Maseras and Spokoyny also reported the synthesis and characterization of dinuclear Pd(I) dimers $[\text{Pd}_2\text{X}(\mu\text{-X})(\mu\text{-P}(\text{tBu})_2\text{Bph})]$ (X = Br or Cl, Bph = Biphenyl) that are catalytically active in Buchwald amination reaction.²³⁶⁻²³⁸

The role of Pd(I) dimers in coupling reactions has been questioned.²²³ In the presence of a salt, OA requires the preliminary fragmentation of $[\text{Pd}^{\text{I}}\text{Br}(\text{PrBu}_3)]_2$ into $[\text{Pd}^0(\text{PrBu}_3)]$ or $[\text{Pd}^0(\text{X})(\text{PrBu}_3)]$ (X = Br, F, OH or $\text{ArB}(\text{OH})\text{O}$) from the Pd(I) dimer, which occurs in the presence of sufficiently nucleophilic additives.^{62,232,239,240}

In the absence of salts, halide exchange between $[\text{Pd}^{\text{I}}\text{Br}(\text{PrBu}_3)]_2$ and 9-iodoanthracene proceeds to form 9-bromoanthracene and $[\text{Pd}^{\text{I}}(\text{PrBu}_3)]_2$.²⁴¹ This proves that the

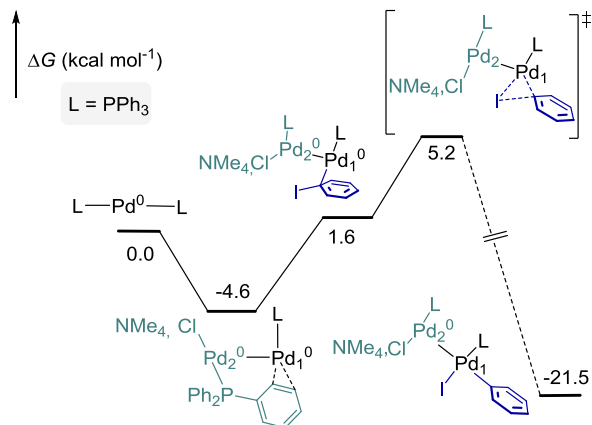
activation of C-I bond is possible on Pd(I)-Pd(I) complexes. Based on ^{31}P -NMR monitoring and DFT calculations (Scheme 30), an halide exchange mechanism was proposed, involving *i.* concerted OA of iodobenzene to Pd(I); *ii.* Br and $\mu\text{-I}$ exchange, *iii.* first RE to release ArBr, *iv.* second OA and *v.* second RE to produce $[\text{Pd}^{\text{I}}(\text{PtBu}_3)]_2$.



Scheme 30. Gibbs energy pathways (ΔG , kcal mol $^{-1}$) for the Br-I halide exchange reaction between iodobenzene and $[\text{Pd}^{\text{I}}\text{Br}(\text{PtBu}_3)]_2$. ΔG are given in kcal mol $^{-1}$. Adapted with permission from reference 241. Copyright 2013 Royal Society of Chemistry.

However, the Pd(I)-Pd(I) dimers that can spontaneously form in solution are not always associated with strong reactivity toward OA. As an illustration, Grimaud, Jutand and Wagschal recently reported that Pd(I)-Pd(I) dimers formed *in-situ* from XPhos/ $[\text{Pd}^{\text{II}}(\text{OAc})_2]$ mixtures are not significantly active in OA steps compared to mono-metallic Pd(0) complex.^{140,242} To date, the origin of this discrepancy has not been elucidated.

Though Pd(I) dimers are now widely described in the literature, OA of aryl halides at Pd(0)-Pd(0) dimers have been much less explored. Based on theory and experiments, the first mechanism of OA at iodoarenes involving two nitrogenated Pd(0) centers has been established by the group of Grimaud in 2017.¹⁰⁹ In this mechanism, the insertion of the first Pd(0) to the substrate. This cooperativity may be encountered with many cross-coupling conditions, especially when stoichiometric amounts of primary and secondary alkyl- and aryl-amines are employed. Perrin and Payard recently studied the effects of NMe_4Cl , on the dimerization and cooperative effect between Pd(0) centers in the OA of PhI using calculations performed at the DFT level.²⁵ The formation of Pd-dimer $\text{NMe}_4[\text{Pd}_2^0\text{Cl}(\text{PPh}_3)_2]$ from $[\text{Pd}^0(\text{PPh}_3)_2]$ and $(\text{NMe}_4)\text{Cl}$ is thermodynamically favorable, in agreement with previous suggestions from Amatore and Jutand (see also section 3.1).³⁰ As shown in Scheme 31, NMe_4Cl and the dimerization improve the ability of Pd(0) to insert into the C-I bond compared to $\text{Pd}^0(\text{PPh}_3)_2$.



Scheme 31. Gibbs energy (ΔG , kcal mol $^{-1}$) pathways for the OA of PhI to electrogenerated $[\text{NMe}_4\text{Pd}_2(\text{Cl})\text{L}_2]$ starting from $[\text{Pd}^0\text{L}_2]$ ($\text{L} = \text{PPh}_3$) and NMe_4Cl used as an energy reference. Adapted from reference 25. Copyright 2022 American Chemical Society.

Pd(I) trimers have also been reported in the literature. The reaction of organic halides with $[\text{Pd}^{\text{I}}_2(\mu\text{-PPh}_2)(\mu_2\text{-OAc})(\text{PPh}_3)_2]$ in THF at room temperature produced Pd trimers $[\text{Pd}_3(\text{X})(\text{PPh}_3)_3(\text{PPh}_2)_2]\text{OAc}$ ($\text{X} = \text{Cl}, \text{Br}, \text{I}$) characterized by MS-ESI and ^{31}P -NMR.² The structure of the phosphide-containing Pd(I) trimer $[\text{Pd}_3\text{Cl}(\text{PPh}_2)_2(\text{PPh}_3)_3]^+[\text{SbF}_6]^-$, was characterized by X-ray diffraction and proved active in Suzuki-Miyaura cross-coupling.²⁴³ This complex was first isolated and characterized by IR and NMR in 1968 by Dixon and Rattray.²⁴⁴ Nevertheless, this complex does not spontaneously undergo OA to Ph-Br or Ph-I bond since Br-to-Pd(I) transmetalation is faster than the direct OA which was attributed to the steric hindrance at Pd centres and 4/3 formal oxidation state. The resulting aryl-Pd(I) intermediate then undergoes OA with Ar-X.

Conclusion

An impressive wealth of knowledge has been accumulated in almost five decades of research on the OA of organic electrophiles to low-valent Pd(0)/Pd(I) species, not only from the point of view of pure organometallic chemistry but also by chemists aiming at understanding and improving catalytic applications. The nature of the ligands is clearly one of the key factors influencing the OA process, but it is now well established that other species normally present in catalytic conditions (cations, anions, nitrogen-containing compounds, alkenes, ...) can have an impact on this elementary step that is at the basis of so many catalytic reactions and that are now part of the standard synthetic chemists' toolbox.

While the fundamentals of the OA reaction under controlled conditions are generally well understood for model Pd complexes, the complexity of real-life catalytic systems - often involving pre-catalysts, additives, diverse Pd sources and structurally complex reaction substrates - is overwhelming. Modern techniques of analysis such as Extended X-ray Absorption Fine Structure Spectroscopy (EXAFS) and molecular modelling at the quantum level will help to bring insight in the dynamic structure of the representative key intermediates in solution, in the condition of catalysis. Having access to such information will bridge the gap with the current knowledge raised on model system. Noteworthy, the current exploration of structure and reactivity of polynuclear and higher order Pd clusters is maintaining active both applicative and fundamental aspects of Pd-mediated organic chemistry.

These most advanced synthetic and mechanistic investigations will be most likely accompanied by current developments in data-driven methods. Actually, the synthetic chemist's toolbox has acquired new predictive tools that hold significant promise for the rapid optimization of the most suitable ligand/pre-catalyst combination.

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The manuscript was written through the contributions of all authors. [¶]These authors contributed equally.

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SYNOPSIS TOC

