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The detailed understanding of reactions involving transition metals requires exact knowledge of the structure of reactants, catalytic species and reaction intermediates. Unfortunately, the ability of metals to form polynuclear complexes does not make it straightforward.¹ Thus, most of the reaction schemes use simplified reactions that reduce the mechanism to mononuclear species. Such a simplified view is useful for a basic understanding of the processes occurring during the reactions. However, for further development in the area of transition metal chemistry the precise nature of the key reaction species should be known. We have chosen the C–H activation reactions catalyzed by palladium(II) carboxylates as the illustration of this issue.

Most of the reaction schemes as well as mechanistic studies are based on monopalladium species. Nowadays, the AMLA/CMD (ambiphilic metal–ligand assisted/concerted metalation deprotonation) mechanisms are used for the explanation of the C–H activation step in reactions involving palladium carboxylates (Scheme 1).² In principle, a molecule of substrate coordinates to the palladium carboxylate in the first reaction step. Next, in the concerted step the reaction center is attacked by a palladium atom while one of the coordinating carboxylates starts to make a new bond with the releasing proton. This leads to the formation of monopalladacycles that in most cases dimerize to form stable C–H activated binuclear complexes.³ However, the ability of palladium carboxylates to form polynuclear complexes opens the way for other reaction mechanisms based on bi or trimetallic species.

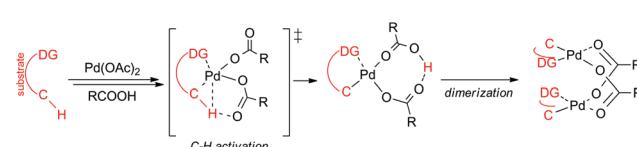
It can be expected that the nuclearity of the species involved in the reaction pathway is influenced by the nuclearity of starting materials. Thus, the first question to be answered is: what is the structure of the catalyst or precatalyst entering into the reaction with the substrate?

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Bi and trinuclear complexes in palladium carboxylate-assisted C–H activation reactions

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The role of polynuclear species in C–H activations assisted by palladium carboxylates has not been clear so far. The summary of the key findings covering this issue shows its important role under certain conditions. However, much more effort is necessary for a deeper understanding of the whole issue.



Scheme 1 Simplified reaction mechanism of remote group directed C–H activation reaction.

Structure of palladium(II) carboxylates

Palladium acetate alone or its combination with carboxylic acids occupies one of the leading positions among transition metal catalysts or catalytic systems. In 1965, Wilkinson⁴ proposed and in 1970, Skapski^{5a} determined its structure to be trimeric cyclic $\text{Pd}_3(\text{OAc})_6$ **1** in the solid state (Fig. 1). Subsequent research showed that the trimeric cyclic structure remains preserved in the solution. However, there is possible solvent-dependent equilibration with its monomeric or dimeric form.⁶ Since then, most of the reaction mechanism proposals involve the formation of monopalladium species that enter into further molecular transformations.

However, in the course of time and increasing popularity of palladium acetate chemists observed different reactivities of catalysts dependent on how the palladium acetate was prepared. This nontrivial behavior⁷ led to a series of studies in which a polymeric form and possible impurities formed by substitution of one acetate ligand for OH^- **2a**, OR^- **2b** and NO_2^- **3** were isolated (Fig. 1).⁸ These species showed

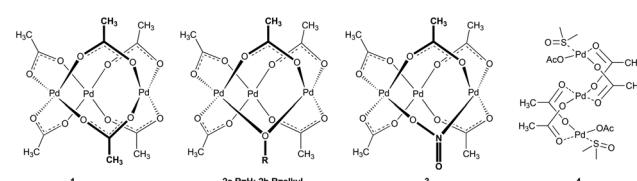


Fig. 1 Products of the reaction of palladium acetate with nucleophiles.

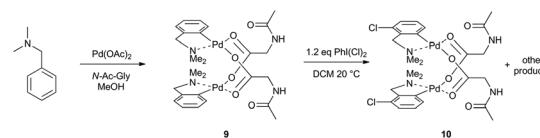


different reactivities in comparison with pure trimeric cyclic palladium acetate. Further questions concerning the structure and nuclearity of precatalysts arose by the introduction of reaction protocols using the combination of palladium acetate with other carboxylic acids. The most favored is the protocol popularized by Fujiwara using the addition of trifluoroacetic acid (TFA) to the reaction system.⁹ Batsanov showed $\text{Pd}_3(\text{OTFA})_6$ to be a cyclic trimer in the solid phase^{5b} while Wilkinson observed palladium trifluoroacetate to be monomeric in ethylacetate.⁴ Furthermore, the monopalladium $[\text{Pd}(\text{OTFA})_2(\text{HOAc})_2]$, $[\text{Pd}(\text{OTFA})]^+$ and $[(\text{OTFA})_2\text{Pd}(\text{TFA})_3]^+$ complexes were proposed to be active species in different reactions.¹⁰ On the other hand, sequential ligand exchange leading to the formation of cyclic trinuclear $\text{Pd}_3(\text{OTFA})_6$ in dichloromethane was recently described in detail.¹¹ Next, coordinating solvents like DMSO or acetone cause the opening of the cyclic trinuclear species giving the linear ones 4 (Fig. 1) or cause fragmentation to mono and dipalladium species.^{4,12} These observations suggest that the composition and nuclearity of the precatalyst is highly influenced by solvent and the purity of starting materials.

Binuclear species

The existence of palladacycles in binuclear dimeric forms motivated research to study the possibility of C–H activation proceeding *via* binuclear species. Musaev *et al.* in their computational study thoroughly examined the structures of the dimeric palladium acetate catalyst as well as their reactivity in the C–H activation of various substrates.¹³ They found that the C–H activation reaction pathway involving binuclear complexes is a little bit disfavored when compared to the mononuclear one. Next, they explained a preferred formation of dimeric palladacycles from monomeric ones due to ligand interactions (π – π stacking) and bridging acetate interactions.

Different results were shown in the work of Vicente, Jones *et al.*¹⁴ that were further extended by Granell, Martínez *et al.*¹⁵ The authors experimentally studied the C–H activation of primary benzylamines in the solid state and solution (Scheme 2). They showed that the reaction of benzylamine (BnNH_2) with palladium acetate leads to the formation of the monometallic nonactivated precomplex $\text{Pd}(\text{OAc})_2(\text{BnNH}_2)$ 5 that upon treating with palladium acetate dimerizes to the precomplex $[\text{Pd}(\text{OAc})(\mu\text{-OAc})(\text{BnNH}_2)]_2$ 6. The following C–H activation step proceeds solely on these dimers in a cooperative manner where the metalation by the first palladium atom is the rate limiting step. The C–H activated product is initially



Scheme 3 C–H activation and functionalization of dimethylbenzylamines in the presence of MPAA.

formed in its “open book” form 7 and then transforms to the stable complex 8.

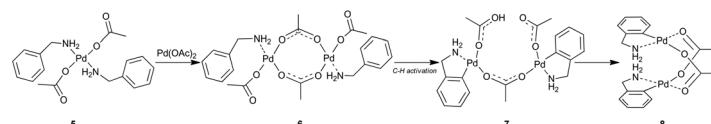
Recently, Musaev, Lewis *et al.* thoroughly examined the effects of mono-*N*-protected amino acids (MPAA) in the C–H activation of dimethylbenzylamines (DMBA-s) (Scheme 3).¹⁶ The binuclear complexes 9 analogous to 8 containing bridging MPAA instead of acetates were synthesized. Furthermore, it was shown that these dimeric complexes in the presence of iodobenzene dichloride undergo subsequent C–H functionalization to give other chlorinated dimeric palladacycles 10. The fact that a bi-palladium reactant is transformed to a bi-palladium product led authors to computationally examine and compare the potential mononuclear and binuclear reaction pathways. DFT calculations performed on the model $2\text{-CF}_3\text{-DMBA}$ substrate show that cyclopalladation on the dimer occurring *via* two sequential CMD steps is both kinetically and thermodynamically favored over the monomeric pathway. Similar to the work of Granell, Martínez *et al.*¹⁵ the first cyclopalladation is a rate-limiting step and facilitates the second cyclopalladation.

Finally, Henry experimentally showed that contrary to the mononuclear $\text{Na}_2\text{Pd}(\text{OAc})_4$ the binuclear $\text{Na}_2\text{Pd}_2(\text{OAc})_6$ is the active precatalyst in the C–H activation of olefins.¹⁷

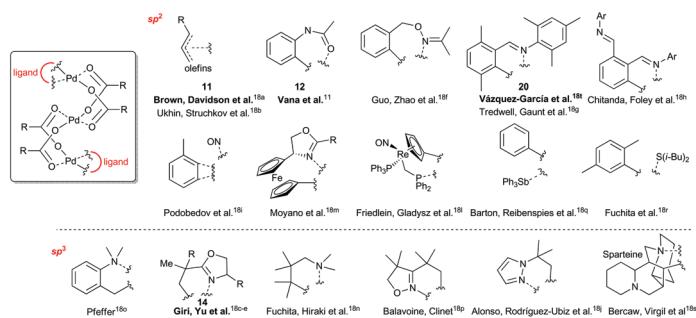
Trinuclear complexes

Over time, several complexes containing linear trinuclear palladium carboxylate motifs together with C–H activated ligands have been observed and characterized.^{11,18} These $\text{C}(\text{sp}^2)\text{H}$ and $\text{C}(\text{sp}^3)\text{H}$ activated complexes are summarized in Fig. 2. Analysis of the reaction conditions and stability of the compounds points to several common features.

In all cases, the reaction conditions require a sub-stoichiometric or stoichiometric amount of substrate as compared to the amount of palladium carboxylate. Next, with the exception of olefins, all these complexes are relatively unstable. Finally, in many cases these complexes are found in combination with their binuclear analogues. There are only few studies reporting



Scheme 2 C–H activation of benzylamines.



palladium atoms in polynuclear species during the C–H activation step? Can C–H activation involving polynuclear complexes lead to different regioselectivities in comparison with the mononuclear pathway?¹⁹ How are reactivity and nuclearity influenced by the addition of carboxylates of different metals?²⁰ What is the role of polynuclear complexes in the ongoing catalytic cycles of C–H functionalization reactions, where their formation is less probable? Answering all these and other related questions will require a lot of effort. However, we believe that this effort is crucial and will be reaped in the design of new catalysts and catalytic reactions and in many other ways.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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