



PERSPECTIVE

'Homeopathic' palladium catalysis? The observation of distinct kinetic regimes in a ligandless Heck reaction at (ultra-)low catalyst loadings



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ABSTRACT

The catalytic behaviour of 'ligandless' palladium(II) acetate in the Heck arylation reaction of iodobenzene with methyl acrylate is examined at (ultra-)low catalyst loadings using *in situ* spectroscopy. The study reveals two distinctive kinetic regimes with distinct Pd orders. A simplified microkinetic model revealed the presence of at least two kinetically competent catalysts, represented by a monomeric (Pd₁) and dimeric (Pd₂) species. The relative catalytic activity and deactivation rates for both species can also be estimated from the experimental results. This work provides direct kinetic evidence that a higher-order Pd species can be more active than a monomeric species, and the key role played by catalyst deactivation, particularly at higher catalyst loadings. This implies that lowering the catalyst loading may be an effective strategy to combat catalyst deactivation without necessarily incurring significant deterioration in reaction rate.

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1. Introduction

The discovery of Pd-catalysed cross-coupling reactions is undoubtedly one of the most significant milestones of synthetic chemistry in the 20th Century. The ability to construct bi-(hetero)aryl scaffolds by C–C bond formation selectively between unsaturated (sp- and sp²-hybridized) carbon centres proliferated the exploration of these molecular motifs in medicinal discovery programs [1]. Consequently, Pd catalysis is widely employed in the manufacturing of many fine chemicals and active pharmaceutical ingredients (API's) [2]. Nevertheless, there are substantial economic, safety and environmental costs associated with the deployment of Pd catalysts in a chemical process; [3,4] not only the price of the metal precursor, its recovery during the purification process, but also the amount of Pd residues present in the products, which are tightly regulated by the pharmaceutical industry.

Among the practitioners of Pd cross-coupling chemistry, it is known that reactions of certain activated aryl halides, particularly aryl iodides and aryl bromides with electron-withdrawing substituents, can be achieved with very high turnover numbers (TON's) in the absence of extraneous ligands. Using Pd(OAc)₂ as a pre-catalyst, we have previously shown that very high turnover numbers in the order of 10⁵–10⁶ can be attained for the Heck arylation reaction between 4 and iodoacetophenone or iodobenzene with acrylate [5]. In the same year, an authoritative review of the Heck reaction was published by Beletskaya and co-workers [6], where the term 'homeopathic doses' of Pd catalysts was first evoked to describe reactions that can proceed with an ultra-low amount of catalyst; exemplified by the Heck coupling reaction between o-iodobenzoic acid and methyl acrylate using 0.0005 mol% (=5 ppm) of Pd(OAc)₂ to achieving the maximum TON of 200,000. Further examples were provided later by two independent research groups [7,8], where the reaction between a number of aryl bromides and olefins was achieved using 'ligandless' Pd(OAc)₂ of between 0.01 and 0.1 mol%. The term 'homeopathic catalysis' was popularised by a number of high-profile publications by de Vries and co-workers [7,9,10], to describe the phenomenon of higher turnover frequencies (TOF's) observed at lower Pd loadings. In their early work [7], it was proposed that lowering the catalyst loading promotes the formation of a more active monomeric catalytically active species, supported by the observation of an anionic PdBr₃⁻ by ES-MS. In recent years, however, there are a growing number of studies suggesting that oligomeric, colloidal, or nanoparticles (NP's) of Pd could also par-

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participate in catalytic reactions; either directly, or as reservoirs for active Pd(0) species. Described by Ananikov and co-workers as a ‘cocktail of catalysts’ [11], the role of these palladium species in cross-coupling reactions remains a hotly debated subject.

In this study, the Heck coupling between iodobenzene (**1**) and methyl acrylate (**2**) in the presence of triethylamine and ‘homeopathic’ levels of Pd (Scheme 1) was chosen as the model system for the present study, for the following reasons:

1. The reaction was extensively studied within our research group [5,12], and is known to proceed using homogeneous or heterogeneous Pd precursors under ‘ligand-free’ conditions, to afford very high turnover numbers and turnover frequencies [6,13], thus providing an ideal model reaction to interrogate the presence of any ‘homeopathic effect’;
2. The reaction progress can be easily monitored by using *in situ*-FTIR spectroscopy. Both the consumption of **1** and the formation of the cinnamate product (**3**) can be monitored by unique absorption bands in the fingerprint region (in this case, these rates are identical as the reaction is 100% selective); and
3. The reaction aliquots can be thermally quenched very effectively [13] to provide independent offline verification of the *in-situ* quantification method (IR).

The reaction kinetics of the Heck coupling between **1** and **2** had been previously examined under a variety of reaction conditions. An early report by Zhao *et al.* [14] utilizes the ubiquitous combination of Pd(OAc)₂/*n*PPh₃ (1 mol% [Pd] loading; *n* = 2), where the initial rate of the reaction was found to be dependent on the initial concentrations of aryl iodide, olefin and base (NEt₃). Subsequently, it was found that the phosphine ligand has a negative effect on the reaction rate, *i.e.* the maximum rate was recorded when *n* = 0. However, the absence of the ligand led to the ‘precipitation of Pd’ (presumably, the formation of Pd black), and the role of the PPh₃ was proposed to promote catalyst stability (TON) at the expense of reaction rate (TOF). Since then, similar studies on the Heck reaction have been performed by others using different Pd precursors, including: a C,N-palladacycle [15], a PNP pincer Pd complex [16], and a phosphine-free catalytic system Pd(OAc)₂/dimethylglycine [17]. Despite the different conditions, the authors unanimously concluded that these metal complexes merely act as reservoirs/precatalysts for highly catalytically active forms of palladium. Notably, all of these studies were conducted with relatively high amounts of [Pd] (0.1–1.5 mol%). As far as we can ascertain, there are no known reports of kinetic studies of Heck arylation reactions performed with Pd loadings of < 0.1 mol%. Also, while the presence of more than one catalytically active species had been proposed in recent years [18], this had not been verified by kinetic experiments.

2. Results and discussion

In this work, rigorous measures were undertaken to take account of: (i) the need to dispense very small amounts of the Pd precursor (<0.1 mg) accurately into each reaction vessel; (ii) eliminate ‘phantom’ catalytic activities caused by residual Pd in the apparatus; [19] and (iii) consistent order and timings of the addition of the reaction components (Fig. S2 and discussions in the Supporting Info). The resultant procedure afforded kinetic data that can be replicated across different batches of the Pd salt, even in different laboratories [20]. Using the standardized protocol, the reaction proceeded instantaneously, without any noticeable induction period. TON’s of up to 9,800 can be attained in DMF in under 2 h using 0.01 mol% (100 ppm) of Pd(OAc)₂ at 110 °C [21,22]. The choice of solvent is known to have a profound effect on the performance of Pd catalysts [22]. In contrast, reactions in toluene and acetonitrile have much lower conversions compared to the reaction performed in DMF (Fig. 1), suggesting that the catalyst is much less stable in these less polar solvents.

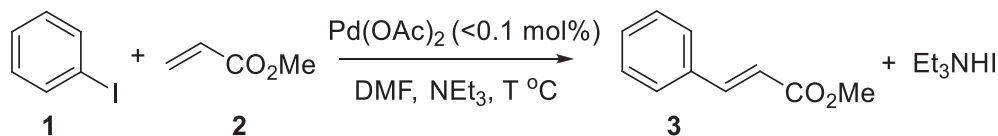
2.1. RPKA experiments

A series of Reaction Process Kinetic Analysis (RPKA) experiments [23,24] were initially performed, to establish the global reaction orders of the various reaction components and catalyst deactivation. Earlier kinetic experiments, performed at higher catalyst loadings, often reported a positive order of dependency between the rate of the reaction on [PhI]. In this case, however, good overlaps of time-normalized reaction profiles of ‘same excess’ and ‘different excess’ experiments can be obtained at 50 ppm catalyst loading (0.005 mol %), showing that the reaction rate is not affected by catalyst deactivation, nor is it dependent upon the initial concentrations of PhI (Fig. 2). Subsequently, the reaction rate is also found to be independent of [acrylate] and [triethylamine] (Fig. S5 and S6, Supporting Info). This is perhaps not surprising that saturation kinetics is observed in the presence of a large excess of substrates. Therefore, the TOF of the system can be represented by eqn (1), where k_{obs} is the pseudo rate constant, and Pd_{tot} is the amount of Pd employed for the reaction.

$$TOF = k_{obs}[Pd]_{tot}^x \quad (1)$$

2.2. Catalyst deactivation

The RPKA experiments showed a good overlap between the control and ‘same excess’ experiments (Fig. 2). Hence, catalyst deactivation is not competitive at such low catalyst loadings (50 ppm). To illustrate this further, a different set of experiments was subsequently devised, whereby a mixture of the reactants (iodobenzene, methyl acrylate and triethylamine) was added in four separate but equal portions (‘doses’ 1–4) sequentially to a solution containing 100 ppm or 1000 ppm of the Pd precursor. At 100 ppm of [Pd], each dose of fresh reactants was consumed with similar rates within 2 h (Fig. 3A), showing that the catalyst does not deactivate significantly. In contrast, at a higher concentration (1000 ppm) of [Pd] (Fig. 3B), while the first dose of reactant (**1**) was consumed very quickly in < 10 min, the formation of Pd black is clearly visible upon the addition of the reactant. Subsequent reactions (**2**) and (**3**) were considerably slower: completing in 2 h, to 11 h, and > 20 h, respectively. These experiments established a direct correlation between catalyst loading and deactivation, concurring with the prevailing theory that the aggregation of Pd as the primary pathway of catalyst deactivation. What is particularly interesting to note is that the process can be effectively suppressed by lowering catalyst loading.



Scheme 1. Heck coupling between iodobenzene and methyl acrylate.

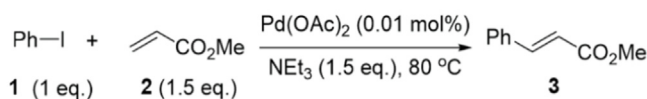
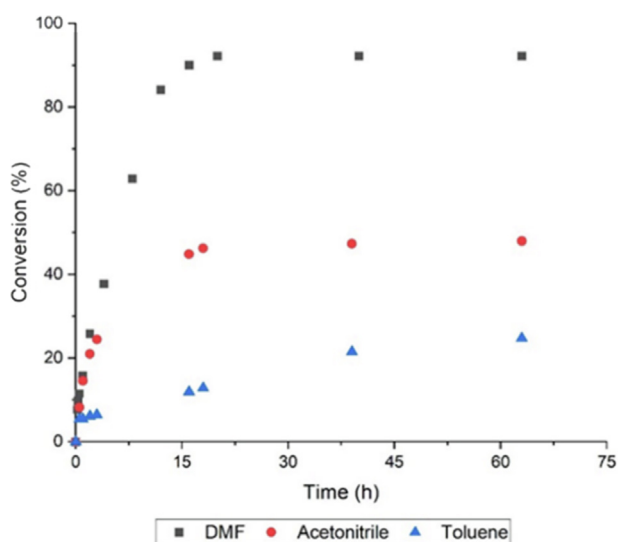


Fig. 1. Reaction profiles of the Heck reaction catalyzed by Pd(OAc)_2 (100 ppm, corresponding to 0.01 mol% Pd loading) in different solvents at 80 °C, conversions monitored by quantitative HPLC.

2.3. Variable time normalisation analysis (VTNA): Change in order in Pd

In this part of the work, we set out to determine the catalyst order (value of x in the global rate equation (1)), which should reveal insights to the nature of the active catalyst species, or its speciation during the catalytic process. For this, another visual kinetic method, expounded in 2016 by Bures, known as ‘variable time-normalisation analysis’ (VTNA) was deployed [25,26]. In contrast to the initial rate method, this approach considers the entire reaction profile, by fitting the power rate law to attain the best fit to the experimental data.

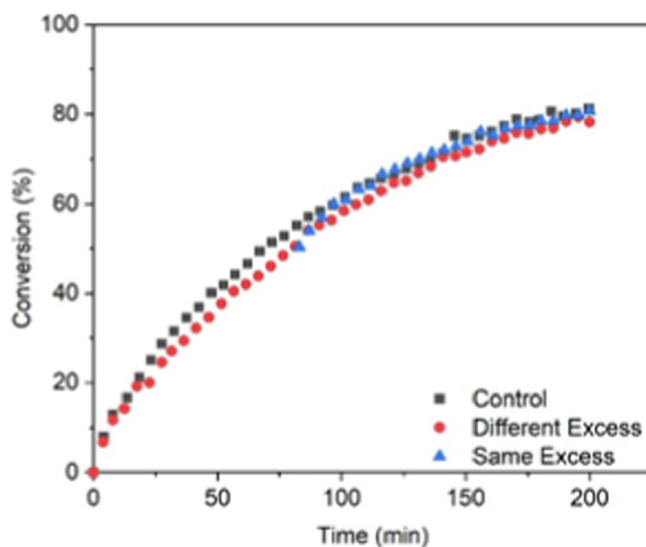


Fig. 2. Visual plots for ‘same excess’ and ‘different excess’ RPKA experiments (50 ppm $[\text{Pd}]_{\text{tot}}$), showing no discernable catalyst deactivation, and zero order dependency of global reaction rate on [1].

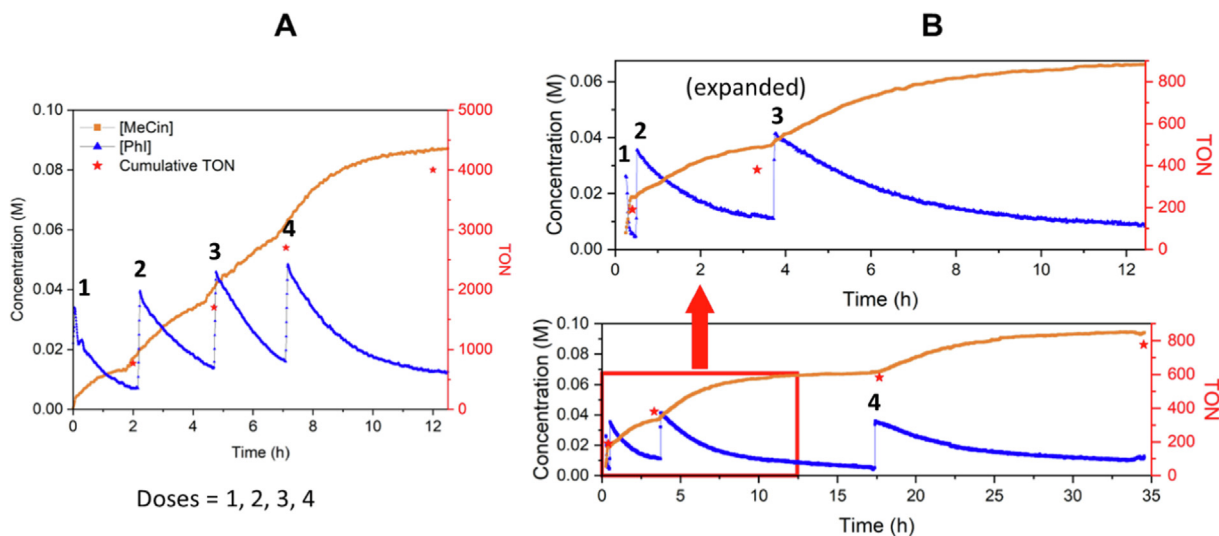


Fig. 3. Consecutive reactants dosing (1–4) to A = 100 ppm [Pd]; B = 1000 ppm [Pd].

Using this method, we uncovered two distinct kinetic regimes in accordance with the change in TOF observed in Fig. 1. At catalyst loadings between 200 and 1000 ppm, $x = 0.9$ produced the best fit (Fig. 4A), while $x = 1.7$ produced the best fit at lower loadings between 30 and 200 ppm (Fig. 4B) [27].

The observed change towards a *higher* Pd order at *lower* catalyst loading is both surprising and counter-intuitive, as this suggests a greater contribution to the rate of turnover by a multinuclear catalyst at lower catalyst loadings. In earlier studies, whenever the involvement of monomer–dimer equilibrating species was reported, the dimer is often found to be inactive (or at least kinetically non-competitive), and serves merely as a ‘reservoir’ for catalytically active monomeric Pd.

At this juncture, it is important to address an alternate explanation, where the change to higher catalyst order may be caused by the presence of a persistent amount of impurity in the reaction system that is poisoning the catalyst, and which is only observable at low Pd loadings [28]. To test this hypothesis, different amounts of [Pd] were subtracted from $[Pd]_{\text{tot}}$, to see whether $x = 1$ can be established for eqn (1). A convergence the VTNA profiles towards the catalyst order of 1 can be observed by deducting 33 ppm of Pd from $[Pd]_{\text{tot}}$ for each reaction (thus adjusting the effective catalyst loadings ($[Pd]_{\text{tot}}$) from 50, 100 and 200 ppm to 17, 67 and 167 ppm, respectively). However, the overlap was poor (Fig. 5); while values just above and below 33 ppm returned worse fits (30 and 35 ppm, see Fig. S7, Supporting Info). Furthermore, catalytic activities can still be observed at loadings of ≤ 30 ppm, leading us to rule out the existence of a persistent catalyst poison in the system.

2.4. Kinetic modelling

To date, the presence of more than one catalytically active species is often proposed, but never been determined kinetically. Based on the experimental observations above, we were able to construct a microkinetic model consisting of two kinetically competent catalytic species, Pd₁ and Pd₂ in dynamic equilibrium, each contributing a TOF, represented as k_1 and k_2 , respectively (Scheme 2). The mass balance of the catalytic species is accounted by the equation: $[Pd]_{\text{tot}} = Pd_1 + 0.5 Pd_2$, *i.e.*, we assume that Pd₂ behaves essentially as a single-site catalyst.

The modelling was performed with the aim of extracting specific values for k_1 , k_2 , k_3 and k_{-3} , which should remain constant across the entire range of catalyst loadings. On the other hand, as the catalyst deactivation by Pd agglomeration is expected to be a highly complex process involving several Pd species. Following a similar approach by Rothenberg *et al.*, the deactivation of Pd₁ and Pd₂ were modelled as first-order processes [27], each with a ‘apparent deactivation rate’ (k'_4 and k'_5). As the deactivation may involve clustering of Pd, k'_4 and k'_5 are expected to (and are allowed to) vary between different Pd concentrations.

$$\frac{d[PhI]}{dt} = -k_1[PhI][Pd_1] - k_2[PhI][Pd_2] \quad (2)$$

$$\frac{d[\text{cinnamate}]}{dt} = k_1[PhI][Pd_1] + k_2[PhI][Pd_2] \quad (3)$$

$$\frac{d[Pd_1]}{dt} = k_{-3}[Pd_2] - k_3[Pd_1]^2 - k'_5[Pd_1] \quad (4)$$

$$\frac{d[Pd_2]}{dt} = k_3[Pd_1]^2 - k_{-3}[Pd_2] - k'_4[Pd_2] \quad (5)$$

$$\frac{d[Pd_x]}{dt} = k'_4[Pd_2] + k'_5[Pd_1] \quad (6)$$

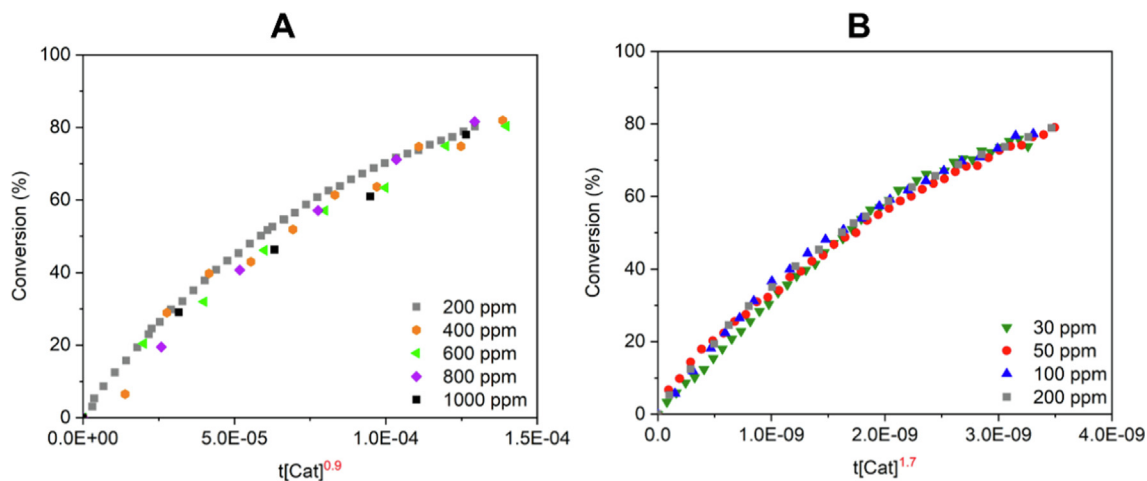


Fig. 4. Catalyst order determined by VTNA at high (A, 200–1000 ppm) and low (B, 30–200 ppm) catalyst loadings.

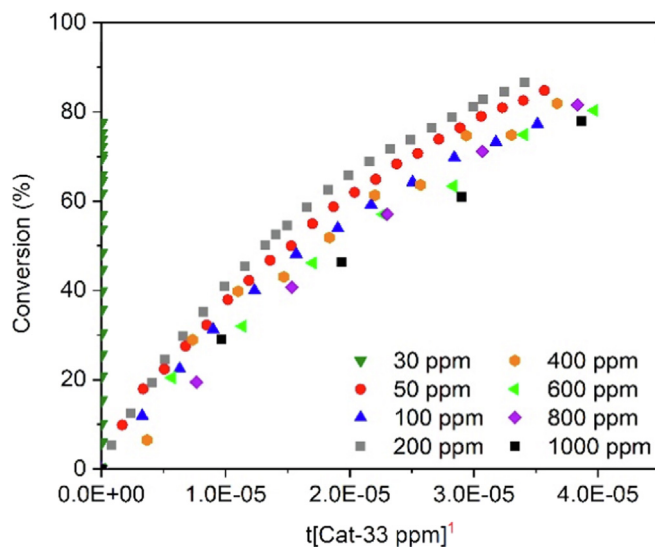
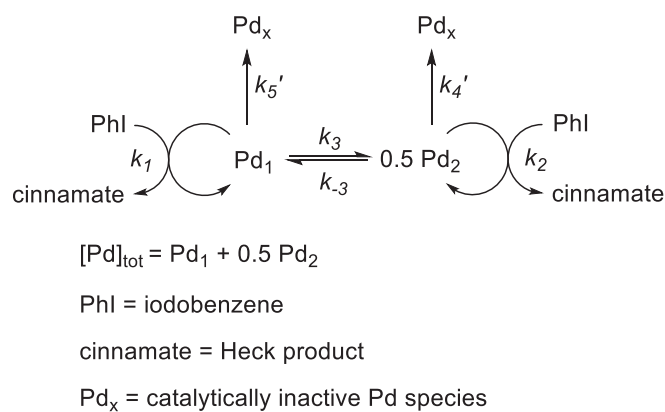


Fig. 5. VTNA reaction profiles fitted to first order Pd, assuming presence of 33 ppm of catalyst poison.

Using an ODE solver, the model was fitted to the data collected in the kinetic experiments, to derive the rate constants. This was performed in two steps: As the experiment data suggests that catalyst deactivation is not significant at low catalyst loadings, the apparent deactivation steps (k_4' and k_5') were omitted initially from the fitting between 30 and 200 ppm of [Pd], where we obtained approximate



Scheme 2. Kinetic model and associated differential equations incorporating two catalytically active species and two (independent) deactivation rates.

values for k_1 , k_2 , k_3 and k_3 . These kinetic constants were further refined in the subsequent fitting to include k'_4 and k'_5 , expanded across the 8 datasets with catalyst loadings between 30 and 1000 ppm under 'standard' conditions (defined in Fig. 2, Run 1). The results for the final fittings are shown in Fig. 6, with the extracted kinetic parameters and root-mean-square deviations (RMSE) shown in Table 1.

Several key insights are revealed by the kinetic modelling, which are summarised below:

1. A reasonably good fit can be obtained with a model containing just two catalytically active species, Pd₁ and Pd₂, as a monomeric and a dimeric single-site Pd species, respectively with an initial ratio of 3:1 for Pd₁:Pd₂, with $[Pd]_{tot} = [Pd_1] + 0.5[Pd_2]$ is inserted in the fitting to account for the material balance. In reality, the involvement of high-order Pd species [30] (trimers, tetramers, etc) cannot be ruled out, as k_2 may be an average TOF of several higher-order catalytic Pd species. In principle, more Pd clusters (trimer, tetramer, etc) could be included to obtain a better fit, but this will lead to overfitting, without necessarily adding any new insight. All attempts to introduce catalytically inactive 'Pd reservoir' or off-cycle species to the model led to poor fits, *i.e.* the total amount of Pd ($[Pd]_{tot}$) speciates entirely into catalytically active species (Pd₁ and Pd₂) upon addition to the reaction mixture.
2. A much more active Pd₂ ($k_2/k_1 = 91$): nearly two orders of magnitude greater than that of the monomeric Pd₁, *i.e.* the dimeric Pd₂ is catalytically more active than Pd₁. Given that we consider Pd₂ as a single site catalyst, this would imply that the two Pd atoms may be working cooperatively [31].
3. Conversely, the deactivation of the monomeric Pd₁ (k'_5) is negligible, while the deactivation of Pd₂ (k'_4) increases significantly with higher amount of $[Pd]_{tot}$. Hence, at load catalyst loadings where $[Pd]_{tot} < 100$ ppm, k'_4 is significantly slow, the catalytic turnover is dominated by the more active Pd₂, resulting in the observation of a higher order of Pd. When $[Pd]_{tot} > 100$ ppm, k'_4 becomes significant, Pd₁ overtakes Pd₂ as the predominant catalytic species, reflected by the decreasing in the order of Pd towards 1.
4. It is important to note, at this juncture, that the catalyst was introduced, as a stock solution, to the solution containing the reactants, which were heated in a jacketed reaction vessel at the required temperature. In almost all cases, catalytic reactions commenced immediately without any induction period. The only exception to this is the reaction performed with 30 ppm of [Pd] (0.003 mol% loading), where the rate in the initial stage of the reaction profile is slower than that predicted by the model (Fig. 6, green line). This could indicate the onset of an induction period. Thus, additional processes may need to be considered for reactions catalysed by < 50 ppm (<0.005 mol%) of [Pd] to account for the formation of the active catalytic species.

A particularly notable feature of the kinetic model is the distribution between Pd₁ and Pd₂ species during catalytic turnover. The microkinetic model reveals that the initial 3:1 ratio rapidly evolves in the initial stages of the turnover into a quasi-steady state equilibrium which is maintained throughout the reaction (Fig. 7).

Attempts to change the initial 3:1 ratio included changing the initial Pd concentration of the stock solution, or by replacing DMF used for the preparation of the stock solution by the less polar toluene, known to alter the equilibrium between monomeric, dimeric and trimeric species [29], had no effect on the observed rate. The only exception was found when the initial concentrations of the reactants were reduced (Fig. 8A). In this case, a better fit can be obtained by changing the initial ratio of Pd₁:Pd₂ from 3:1 to 18:1 (Fig. 8B), while maintaining all the previously derived kinetic rate constants. Although the fit is not perfect, this does suggest that the Pd monomer to dimer ratio is directly affected by [PhI].

This led us to speculate that the ratio reflects a partitioning of reactive intermediates within the first few catalytic turnovers, rather than the pre-catalysts in the stock solution. As the oxidative adduct is often the thermodynamically more stable reactive intermediate found in the resting state, a mechanism is tentatively proposed, where Pd₁ and Pd₂ represent two catalytically viable species that are obtained from the oxidative addition of iodobenzene to a $[Pd_n^{(O)}(OAc)_n]^-$ precursor, which is known to exist preferentially as a mixture of monomer and trimer in DMF [29] (Scheme 3). The hypothesis is supported by previous proposals of similar anion-bridged dimeric and trimeric adducts, which had been isolated and shown to be catalytically competent in Suzuki-Miyaura cross-coupling reactions, although their relative catalytic activities were not kinetically quantified [30,32].

Last but not least, the reaction was replicated across different temperatures at 100 ppm of [Pd], where the model suggests that the active catalyst is predominantly Pd₂. Based on initial rates, the Arrhenius plot produced an activation energy of 56.8 kJ/mol and the Eyring plot produced a ΔH^\ddagger of 53.8 kJ/mol (Figs. S8–S10, Supporting Info), which are significantly lower than that previously reported values for Pd(OAc)₂/PPh₃ ($E_a = 96.2$ kJ/mol) [14] and a [CN]-palladacycle ($\Delta H^\ddagger = 69$ kJ/mol); [15] further confirming that ligandless Pd₂ is considerably more active than these ligated complexes.

3. Conclusion

We have identified the presence of more than one catalytically active species in the Heck arylation reaction between iodobenzene and methyl acrylate. Two distinct kinetic regimes were identified in this system: At very low catalyst loading between 30 and 200 ppm, catalyst deactivation is non-competitive within the reaction timescale, and the global rate equation showed an order of 1.7 for [Pd]. In contrast, above 200 ppm, catalyst deactivation started to predominate, accompanied by a reduction of the Pd order to 0.9.

Subsequent kinetic modelling revealed the presence of more than one catalytically active species operating in quasi-equilibrium: nominally a monomeric (Pd₁) and a dimeric (Pd₂) species; with the latter being 90 times more active than the former. Above 200 ppm, however, the dimeric species deactivates rapidly (most probably through agglomeration to form Pd black [34]) and observed turnover may be attributed primarily to the catalytic activity of a monomeric species. The kinetic data allowed us to determine, empirically, the deactivation rates (k'_4 and k'_5). As far as we can ascertain, this is the first time the kinetic profiles have been determined for the Heck arylation reaction at such low catalyst loadings. It will be interesting to extend the work to other cross-coupling processes, such as the Suzuki-Miyaura reaction, which is also known to be proceed in ultra-low levels of Pd [33].

The identification of Pd₁ and Pd₂ by spectroscopic and mass spectrometry is extremely challenging at such low concentrations. It is important to acknowledge the deviation from the model at the lowest catalyst loading of 30 ppm (0.003 mol%). Below this threshold, it became difficult to obtain reproducible kinetic data; specifically, we started to observe the development of a significant induction period at 5 ppm $[Pd]_{tot}$, which varies between experiments. The induction period could indicate the presence of a catalyst pre-activation process,

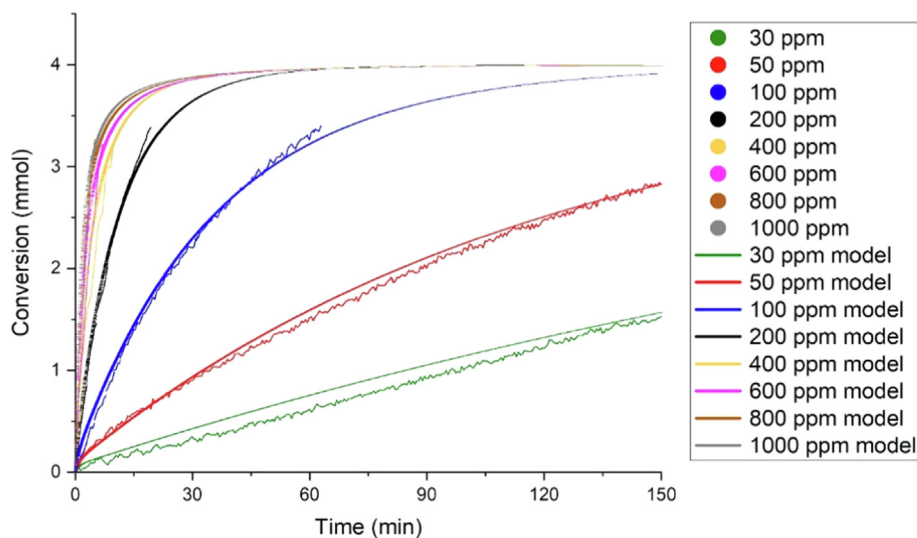


Fig. 6. Fitting of the model to experimental data (expanded between 0 and 150 min; full-fitting was performed between 0 and 400 min, from which the RMSE values in Table 1 were extracted).

Table 1

Kinetic rate constants and RMSE values extracted from fitting the kinetic model (Scheme 2) to experimental results obtained with 30–1000 ppm of [Pd] catalyst.

[Pd] _{tot}	k_1	k_2	k_3	k_{-3}	k_4	k_5	RMSE
30	8.61	790.96	366.9	0.96	1.39×10^{-16}	4.97×10^{-19}	0.106
50					1.16×10^{-4}	8.76×10^{-12}	0.072
100					0.00761	6.15×10^{-15}	0.069
200					0.0296	1.73×10^{-15}	0.093
400					0.142	3.17×10^{-15}	0.273
600					0.247	2.27×10^{-15}	0.311
800					0.322	1.58×10^{-16}	0.409
1000					0.432	1.06×10^{-15}	0.344

which is very susceptible to the presence of trace amounts of impurities at such low loadings, e.g. in the solvent, reagent, or even the presence of O₂ or H₂O [29,34], that are difficult to replicate between experiments.

We have demonstrated in this work, that catalyst deactivation can be effectively suppressed by lowering the catalyst loading. Perhaps even more significantly, we have identified a specific catalytic loading regime where a higher order Pd species (Pd₂) that is modelled to be 90 times more reactive than the monomeric Pd (Pd₁), and with a much lower activation energy compared to ligated Pd complexes. This offers an interesting new alternative paradigm to palladium catalysis: Rather than the usual practice of adding ligands, such as PPh₃, known to suppress catalyst degradation at the expense of reaction rate; it may, instead, be possible to simply lower the catalyst loading without extraneous ligands nor necessarily incurring a penalty in the reaction rate. In terms of process optimization, this means that less Pd can be employed, with the added advantage of simplifying the workup procedure and thus improve the overall sustainability of the process.

Author contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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Data availability

Data will be made available on request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

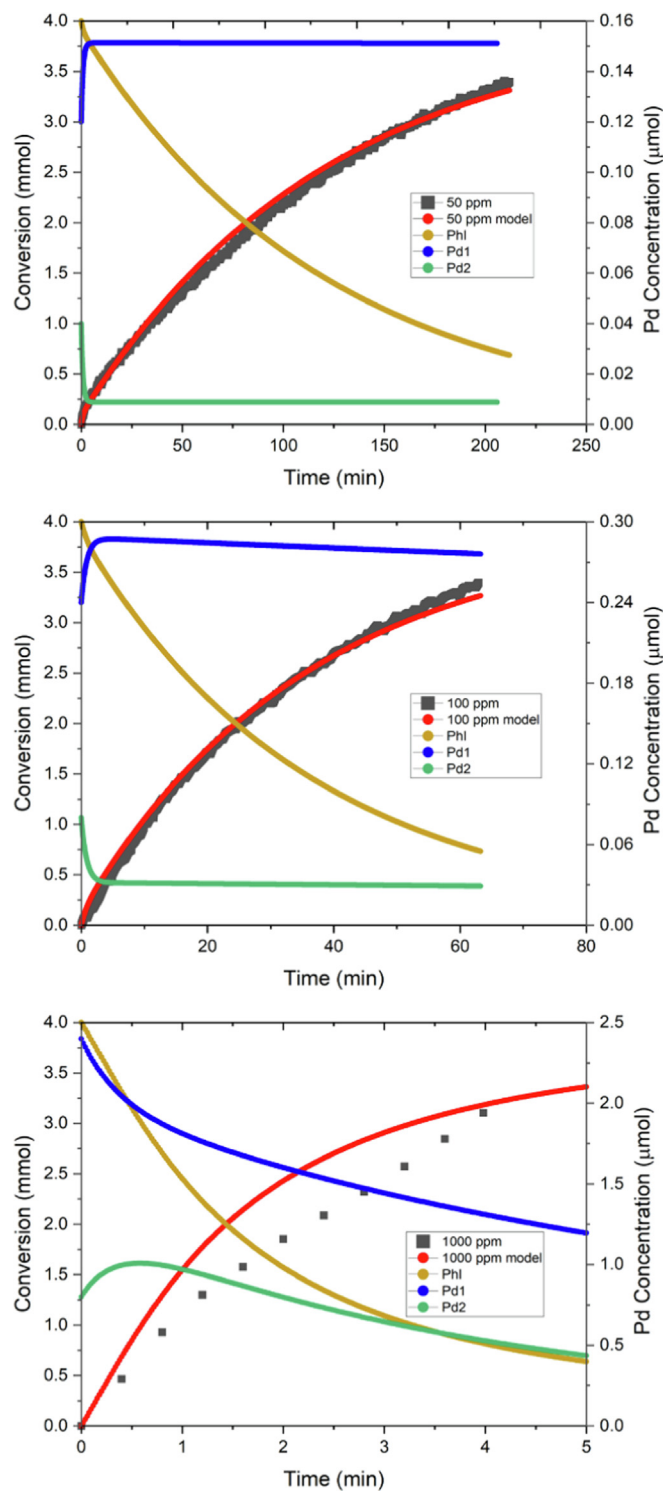


Fig. 7. Evolution of a quasi-equilibrium between Pd₁ and Pd₂ (blue and green lines, respectively), from an initial ratio of 3:1, during the catalytic turnover at 50 (top), 100 (middle) and 1000 (bottom) ppm of $[Pd]_{tot}$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Acknowledgment

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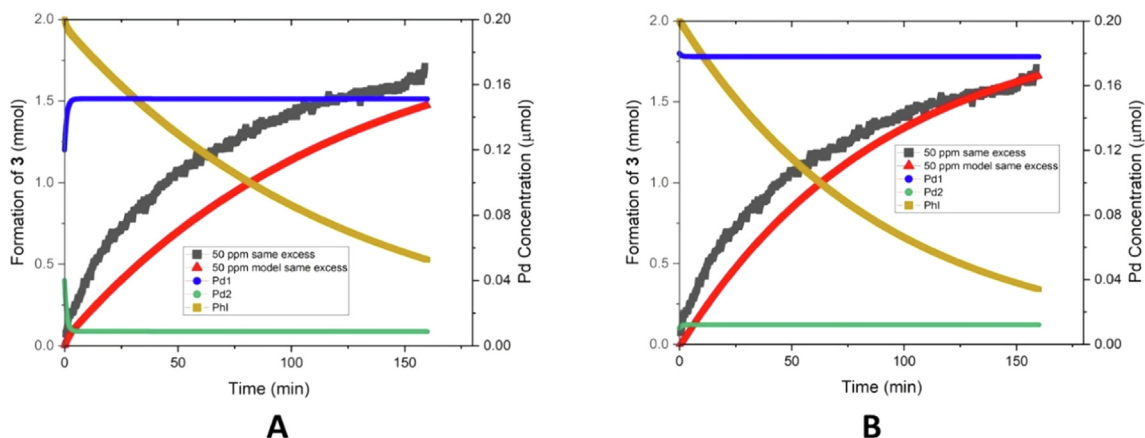
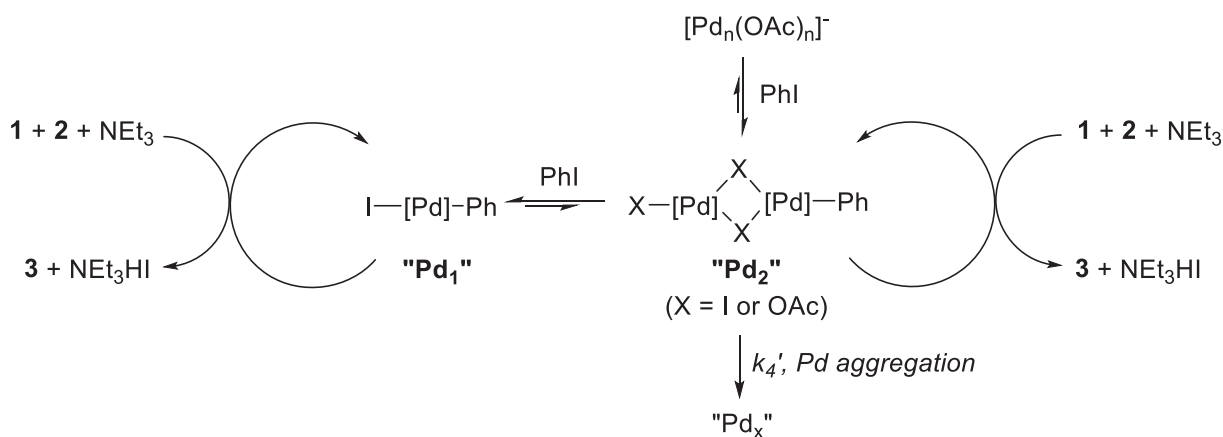


Fig. 8. Fitting of previously extracted kinetic data (k_1 - k_5) to the reaction profile obtained with 50 ppm $[Pd]_{tot}$ under 'same excess' conditions (Fig. 2, Table entry 2): $[PhI] = 0.1$ M; $[2] = [Et_3N] = 0.05$ M.



Scheme 3. Formation of Pd_1 and Pd_2 catalytically active species in a 'ligandless' system.

Appendix A. Supplementary material

Detailed experimental procedures, as well as additional supporting experiments are provided as supporting information. Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jcat.2023.05.005>.

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