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# Aerobic C–H Bond Activation at a Pd Center under Aqueous Conditions

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## Abstract

Recent reports have increasingly documented palladium-catalyzed C–H bond functionalization reactions involving high-valent Pd<sup>III</sup> and Pd<sup>IV</sup> intermediates, yet these transformations often depend on strong oxidants and external bases. Herein, we report a series of Pd<sup>II</sup> complexes [(<sup>p</sup>R<sup>N</sup>3CH)Pd<sup>II</sup>(MeCN)](BF<sub>4</sub>)<sub>2</sub>, supported by a tetradentate pyridinophane ligand, that undergo aerobic C–H bond activation under mild aqueous conditions without the need for an added external base to generate isolable Pd<sup>III</sup> complexes. In this transformation, O<sub>2</sub> serves as both an oxidant and proton acceptor, eliminating the need for an exogenous base. Mechanistic and computational studies are consistent with a rate-limiting concerted metalation-deprotonation (CMD) pathway involving a key Pd–O<sub>2</sub> species that promotes C–H bond activation. Notably, the presence of water in the solvent mixture and slightly elevated temperatures enhance reactivity and lead to quantitative formation of the Pd<sup>III</sup> product, improving its synthetic utility. Overall, this study



establishes a C–H bond activation pathway at high-valent palladium centers that proceeds without added external base, with O<sub>2</sub> serving as both oxidant and internal proton acceptor. These findings provide key insights into high-valent palladium reactivity and lay a mechanistic foundation for sustainable aerobic oxidation strategies.

## Introduction

The importance and versatility of Pd-catalyzed C–H activation reactions in the synthetic community have been well documented over the past several decades.<sup>1-7</sup> More recently, oxidative C–H activation pathways involving high-valent Pd<sup>III</sup> and Pd<sup>IV</sup> intermediates have attracted significant attention.<sup>1, 8-13</sup> In this context, our group has also explored C–H activation chemistry mediated by high-valent Group 10 metal complexes supported by pyridinophane ligands.<sup>14-20</sup>

Despite these advances, most high-valent Pd-mediated C–H activation systems rely on strong chemical oxidants and an external base, raising concerns regarding sustainability and functional group compatibility.<sup>21-22</sup> A major challenge in high-valent Pd chemistry is the development of mild and sustainable oxidation strategies that eliminate the need for hazardous reagents, while maintaining mechanistic control over product formation. Molecular oxygen represents an attractive terminal oxidant owing to its abundance and environmental compatibility especially in Pd-catalyzed C–H functionalization.<sup>23-34</sup> Notably, the Yu group has reported several prominent examples of Pd-catalyzed C–H functionalization reactions, utilizing O<sub>2</sub> as an oxidant across a broad range of reactions.<sup>31, 35-37</sup> However, most O<sub>2</sub>-based Pd<sup>II</sup> systems still require an external base, typically acetate, to facilitate C–H bond activation.<sup>35-36</sup> Developing a system that operates without an added external base, in which O<sub>2</sub> serves as both the oxidant and the proton acceptor, would represent a significant conceptual advance. Water is an appealing medium in this regard due to its



abundance and hydrogen-bonding properties,<sup>38-42</sup> however, its role in high-valent Pd-mediated aerobic C–H bond activation remains poorly understood.<sup>36, 43-48</sup> Additionally, previously reported O<sub>2</sub>/H<sub>2</sub>O systems often require elevated temperatures or prolonged reaction times, limiting their practicality, and key mechanistic details including the interaction between Pd and O<sub>2</sub> and the nature of the transient high-valent Pd/O<sub>2</sub> intermediates remain unresolved.<sup>38, 49</sup>

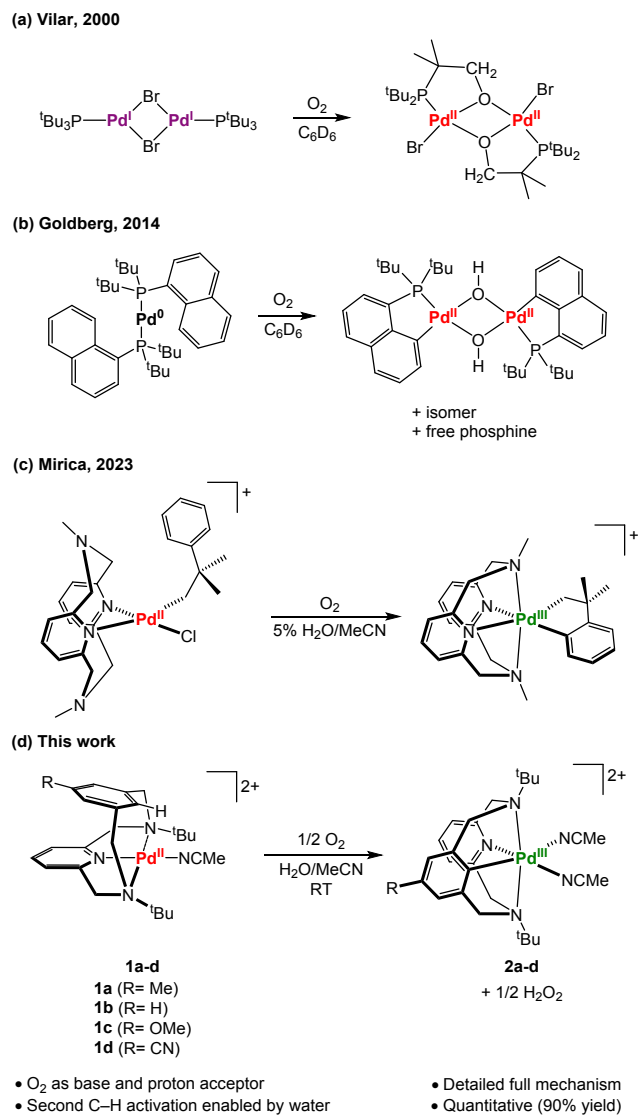
Several studies have described aerobic C–H bond activation at Pd centers in the absence of an external base (Figure 1). For example, Vilar and coworkers demonstrated that a Pd<sup>I</sup> dimer reacts with O<sub>2</sub> to form a C–O bond via C–H bond activation, although the yield of the Pd<sup>II</sup> product and the fate of the C–H-derived hydrogen atom were not fully clarified (Figure 1a).<sup>50</sup> The Goldberg group reported aerobic oxidation of a Pd<sup>0</sup> complex to a Pd<sup>II</sup>-peroxo species, which subsequently promotes C–H activation through a cyclometalated Pd–OOH intermediate (Figure 1b).<sup>51</sup> Our group has also reported Pd<sup>II</sup> complexes that activate C–H bond aerobically through high-valent Pd intermediates (Figure 1c),<sup>18</sup> in addition to aerobically-induced C–C or C–O bond formation reactions via high-valent Pd species.<sup>52-56</sup> While these studies establish the feasibility of aerobic C–H bond activation at Pd, detailed insights into how O<sub>2</sub> interacts with Pd and the C–H substrate without an exogenous base remain limited. In addition, most reported systems rely on low-valent Pd complexes supported by electron-rich ligands that readily react with O<sub>2</sub>. The product yields are typically low, and the fate of the protons and oxygen atoms have rarely been clarified.

Herein, we report the aerobic C–H bond activation of Pd<sup>II</sup> complexes, [(p<sup>R</sup>N<sub>3</sub>CH)Pd<sup>II</sup>(MeCN)](BF<sub>4</sub>)<sub>2</sub>, **1a-d**, at room temperature in aqueous solution, proceeding without exogeneous base to afford isolable Pd<sup>III</sup> complexes [(p<sup>R</sup>N<sub>3</sub>C)Pd<sup>III</sup>(MeCN)<sub>2</sub>](BF<sub>4</sub>)<sub>2</sub>, **2a-d**, in quantitative yield (Figure 1d). While the Pd<sup>III</sup>-aryl complex has been previously reported by our group,<sup>15</sup> its formation via direct O<sub>2</sub>-mediated C–H activation and the quantitative kinetic and



mechanistic framework for this transformation have not been previously reported. Combined kinetic, mechanistic, and computational studies establish that a Pd<sup>III</sup>-superoxo intermediate promotes C–H bond activation through a CMD-like transition state in which a Pd/O<sub>2</sub> species functions as an internal base. Moreover, hydrogen bonding in water lowers the barrier for C–H bond activation steps, enabling pathways inaccessible in non-aqueous media. Use of slightly elevated temperatures shortens the reaction time to ~1 hour, rendering the use of oxygen as an oxidant and proton acceptor more practical. Overall, these findings reveal a mechanistically distinct aerobic C–H bond activation pathway at high-valent Pd centers, with broad implications for the design of future sustainable oxidation strategies.





**Figure 1.** (a-c) Reported aerobic C–H bond activation without an added external base by Pd species from Vilar, Goldberg, and Mirica groups; (d) the reaction of complexes **1a-d** under aerobic conditions reported in this study.

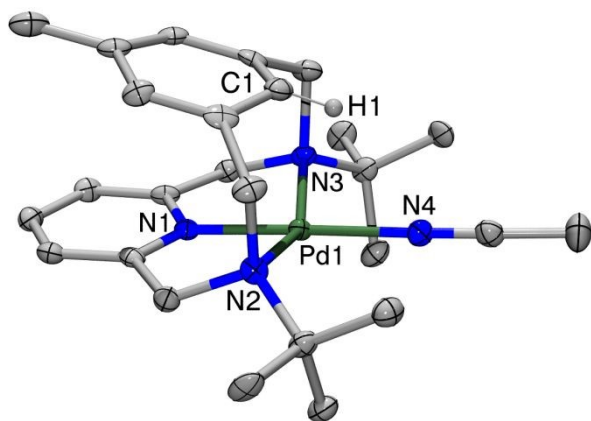
## Results and discussion

### Synthesis and characterization of **1a**



The [(p<sup>Me</sup>N<sub>3</sub>CH)Pd<sup>II</sup>(MeCN)](BF<sub>4</sub>)<sub>2</sub> (**1a**) complex was prepared in 85% yield via the reaction of p<sup>Me</sup>N<sub>3</sub>CH and [Pd<sup>II</sup>(MeCN)<sub>4</sub>](BF<sub>4</sub>)<sub>2</sub>, and X-ray quality orange-colored crystals of **1a** could be obtained from vapor diffusion of diethyl ether into acetonitrile solution at -35 °C. The structure of **1a** reveals a square planar geometry around the Pd center ( $\tau_4 = 0.12$ ), with one pyridine nitrogen atom, two amine atoms, and one nitrogen atom from one MeCN (Figure 2). Interestingly, the Pd⋯H1 distance is 2.393 Å, which is much shorter than in the previously reported complex (p<sup>Me</sup>N<sub>3</sub>CH)Pd<sup>II</sup>(OAc)<sub>2</sub> (2.81 Å),<sup>15</sup> and thus suggesting a stronger Pd⋯H–C<sub>ipso</sub> interaction. The <sup>1</sup>H NMR spectrum of **1a** reveals a distinct peak attributed to the C<sub>ipso</sub>–H proton at 9.45 ppm, which was shifted downfield compared to 7.08 ppm in the free ligand (Figure S5),<sup>15</sup> implying that the Pd⋯H–C interaction can be defined as a weak anagostic interaction.<sup>57</sup> The close interaction of the C–H bond with the Pd<sup>II</sup> center is likely due to a ligand enforced geometry around the metal center,<sup>57–61</sup> while the broad peaks of the methylene groups in the <sup>1</sup>H NMR spectrum indicate the complex is fluxional in solution (Figure S5). Notably, in the same crystal batch of complex **1a** a small amount of yellow crystals were found and determined to correspond to the di-solvento complex [(κ<sup>2</sup>-p<sup>Me</sup>N<sub>3</sub>CH)Pd<sup>II</sup>(MeCN)<sub>2</sub>](BF<sub>4</sub>)<sub>2</sub> (**1ab**, Figure S49), reminiscent of the previously reported (p<sup>R</sup>N<sub>3</sub>CH)Pd<sup>II</sup>(OAc)<sub>2</sub> complexes, and further supporting the fluxional nature of the pyridinophane ligand that can support various coordination geometries around the Pd center.<sup>15</sup> Finally, the cyclic voltammogram (CV) of **1a** exhibits an irreversible anodic peak at E<sub>pa,ox</sub> = 1.09 V vs Fc<sup>+0</sup> and a reversible reductive wave at E<sub>1/2,red</sub> = -0.43 V vs Fc<sup>+0</sup> (Figure S15). The irreversible anodic peak is tentatively attributed to oxidation of the Pd<sup>II</sup> precursor, and the reversible reductive wave is tentatively assigned to the Pd<sup>II/III</sup> redox process. The relatively high oxidation potential may stem from a structural change at the Pd center that is needed to stabilize the Pd<sup>III</sup> center.<sup>62–64</sup>





**Figure 2.** Solid-state structure of dication of **1a** with 50% probability ellipsoids. The counterions and hydrogen atoms were omitted for clarity. Selected bond distances (Å) and angles (°): Pd1–N1 1.947(5), Pd1–N2 2.210(6), Pd1–N3 2.201(6), Pd1–N4 2.011(5), Pd1–H1 2.393, Pd1–C1 2.563(7), Pd1–H1–C1 89.3.

### Oxidative reactivity of **1a**

To investigate C–H bond activation via a high-valent Pd pathway, we examined the oxidative reactivity of **1a** using various oxidants. The addition of  ${}^{\text{A}c}\text{FcPF}_6$  (+0.25 V vs  $\text{Fc}^{+/0}$ ),<sup>65</sup>  $\text{NOBF}_4$  (+0.87 V vs  $\text{Fc}^{+/0}$ ),<sup>65</sup> (thianthrenyl) $\text{BF}_4$  (+0.86 V vs  $\text{Fc}^{+/0}$ ),<sup>65</sup> or  $\text{PhICl}_2$  (–0.9 V vs  $\text{Fc}^{+/0}$ )<sup>66</sup> to a solution of **1a** did not yield any detectable high-valent Pd species, and instead decomposition to Pd black was observed. In contrast, exposure of **1a** to  $\text{O}_2$  (+0.68 V vs  $\text{Fc}^{+/0}$ )<sup>67</sup> or air in MeCN led to the formation of the Pd<sup>III</sup> complex  $[(^{\text{pMe}}\text{N}_3\text{C})\text{Pd}^{\text{III}}(\text{MeCN})_2](\text{BF}_4)_2$  (**2a**, Figure 1d), as confirmed by UV-Vis and EPR spectroscopy (Figures 3a and S18). While the employed oxidants are likely not oxidizing enough to oxidize **1a** (+1.09 V vs  $\text{Fc}^{+/0}$ , Figure S15) via outer-sphere oxidation,  $\text{O}_2$  appears to promote C–H bond activation through a distinct inner-sphere pathway likely involving coordination to Pd, ligand exchange, and structural reorganization steps. Moreover, this



transformation represents a rare example of aerobically promoted C–H bond activation occurring without an added external base.

A structurally related Pd<sup>II</sup>-acetate complex (<sup>p</sup>MeN3CH)Pd<sup>II</sup>(OAc)<sub>2</sub>, which shares the same ligand scaffold as **1a**, did not undergo C–H bond activation under aerobic conditions, even in the presence of excess acetate.<sup>15</sup> The X-ray crystal structure suggests that the binding of the two acetate ligands prevents the positioning of the C–H bond in the proximity of the Pd center for activation. In contrast, complex **1a** features a labile MeCN ligand and adopts a geometry that allows for a shorter Pd⋯H<sub>ipso</sub> distance, 2.393 Å vs 2.808 Å in (<sup>p</sup>MeN3CH)Pd<sup>II</sup>(OAc)<sub>2</sub>, and thus facilitating the O<sub>2</sub>-mediated C–H bond activation. Overall, these observations highlight the crucial role of ligand substitution and structural flexibility in enabling aerobic C–H bond activation.

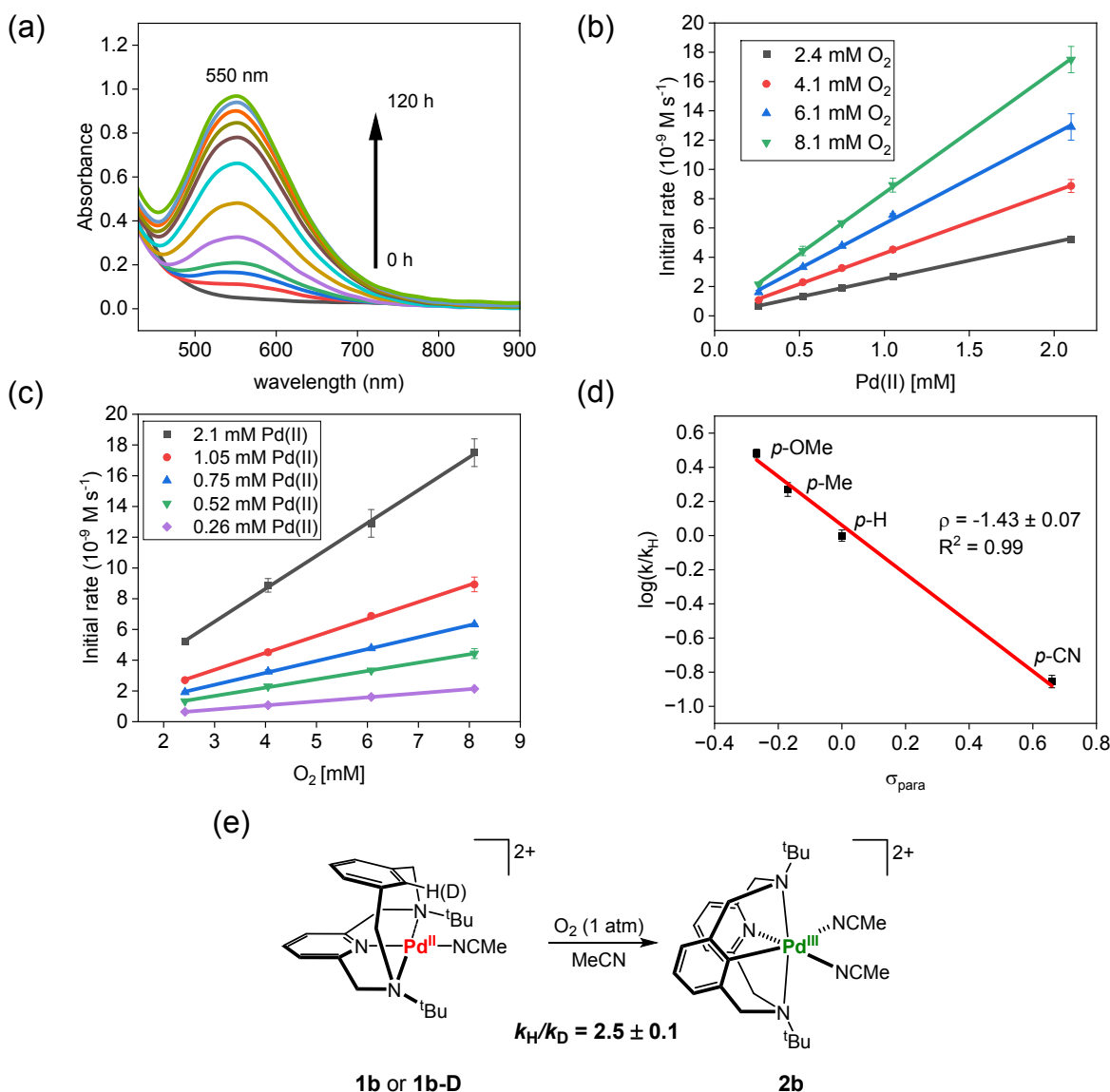
### Kinetics on the aerobic reactivity of **1a**

In order to probe the mechanism of this transformation and the specific role of O<sub>2</sub> during C–H bond activation, we conducted kinetic studies on the aerobic oxidation of [(<sup>p</sup>RN3CH)Pd<sup>II</sup>(MeCN)](BF<sub>4</sub>)<sub>2</sub> complexes **1a-d**. For consistency, the kinetic studies were performed using in situ generated complexes by mixing 1 equiv Pd(MeCN)<sub>4</sub>(BF<sub>4</sub>)<sub>2</sub> with 1 equiv of <sup>p</sup>RN3CH ligand; the detailed experimental procedures are provided in the Supporting Information. We tracked the formation of the product **2a-d** by monitoring the development of the absorbance at 550 nm in UV-Vis (Figure 3a). The kinetic order of the Pd<sup>II</sup> complex (**1a**) and oxygen was investigated (Figures 3b-c). The absorbance peak corresponding to **2a** at 550 nm gradually increased and reached saturation after 96 hours (Figure S20). As the reaction proceeded slowly, the rates of reaction were determined using the method of initial rates,<sup>68</sup> to reveal a first-order dependence on [Pd<sup>II</sup>] at various O<sub>2</sub> concentrations in MeCN (Figure 3b, [O<sub>2</sub>] = 2.4-8.1 mM).<sup>69-70</sup> In addition, first-order kinetics in O<sub>2</sub> was observed at all Pd concentrations (Figure 3c,



[Pd<sup>II</sup>] = 0.26-2.10 mM). Based on the experimental results that the reaction is first-order kinetics in both [Pd<sup>II</sup>] and [O<sub>2</sub>], we conclude that the reaction follows second-order kinetics overall. To ensure the reliability of the initial rate analysis, we additionally performed global kinetic fitting using a second-order rate model with respect to **1a** (Figure S29). The fitting was conducted using the entire time course of the reaction (> 3 t<sub>1/2</sub>), giving a rate constant of  $k_{\text{global}} = 1.01 \times 10^{-3} \text{ M}^{-1}\text{s}^{-1}$ . The value is in good agreement with that obtained from the initial rate method ( $k_{\text{initial}} = 1.05 \times 10^{-3} \text{ M}^{-1}\text{s}^{-1}$ ), and the fitted curve reasonably reproduces the experimental kinetic trace for the formation of product **2a**. In addition, the rate constants obtained under various Pd<sup>II</sup> and O<sub>2</sub> concentrations remain consistent, further supporting the validity of the initial rate method (Figure S7). Given the similar kinetic parameters obtained from initial rate analysis and global kinetic fitting, for simplicity the initial rate method was employed for most kinetic analyses, and all detailed kinetic procedures and fitting methods are provided in the Supporting Information.





**Figure 3.** (a-c) Kinetic analysis of aerobic C–H bond activation of complex **1a** in MeCN at 293 K: (a) UV-Vis monitoring of the formation of **2a**, with a characteristic absorption band at 550 nm, upon the reaction of **1a** (1.05 mM) with O<sub>2</sub> (8.1 mM), (b) Pd<sup>II</sup> dependence ([O<sub>2</sub>] = 2.4–8.1 mM), and (c) O<sub>2</sub> dependence ([Pd<sup>II</sup>] = 0.26–2.1 mM). (d) Hammett analysis of the aerobic C–H bond activation reactions for *para*-substituted complexes **1a-d** (1.05 mM) in O<sub>2</sub>-saturated MeCN (8.1 mM) at 293 K. (e) Kinetic isotope effect determined by independent rate measurements of **1b** (1.05



mM) and **1b-D** (1.05 mM) in O<sub>2</sub>-saturated MeCN (8.1 mM) at 293 K.

### Hammett $\rho$ and Kinetic Isotope Effect (KIE) studies

We next sought to study the electronic dependence of the aerobic oxidation reaction. By comparing the reaction rates of the system described above with those of the modified N3CH analogs, we aimed to evaluate the extent to which *para*-substituents on the reactive C–H bond influence the reaction rate and to elucidate the underlying reaction mechanism. A Hammett analysis was performed by comparing the rates obtained at a Pd concentration of 1.05 mM and O<sub>2</sub> concentration of 8.1 mM (Figure 3d). A  $\rho$  value of  $-1.43 \pm 0.07$  was obtained with a strong correlation ( $R^2 = 0.99$ ), indicating that electron-donating substituents accelerate the reaction. The negative  $\rho$  value is consistent with the development of positive charge in the transition state.

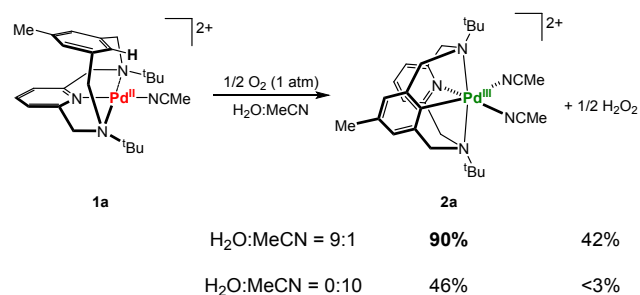
To gain further mechanistic insight, the kinetic isotope effect (KIE) was examined for the reactions of **1b** and **1b-D**, in which the H<sub>ipso</sub> of **1b** was replaced by deuterium. A primary KIE value of  $k_H/k_D = 2.5 \pm 0.1$  was obtained (Figure 3e). This experimentally determined KIE indicates that C–H bond activation contributes to the rate-limiting in this transformation.<sup>71</sup>

The experimentally determined Hammett and KIE values are consistent with those reported for acetate-assisted Pd-mediated C–H bond activation reactions.<sup>72-79</sup> In particular, the observed primary KIE (~2.5) and the Hammett correlation support the involvement of a concerted metalation-deprotonation (CMD)-type C–H activation step. Notably, in contrast to previously reported acetate-assisted systems, the present reaction proceeds without an added external base. These results are therefore consistent with a scenario in which oxygen-derived ligands, such as superoxide or hydroperoxide, function as internal bases and participate in proton abstraction during C–H activation.



### Optimized C–H bond activation under aqueous conditions

Complex  $[(\text{p}^{\text{Me}}\text{N3C})\text{Pd}^{\text{III}}(\text{MeCN})_2](\text{BF}_4)_2$  (**2a**) was independently synthesized and fully characterized, enabling accurate determination of product yields by UV-Vis spectroscopy ( $\epsilon_{550\text{nm}} = 2128 \text{ M}^{-1} \text{ cm}^{-1}$  in MeCN,  $2148 \text{ M}^{-1}\text{cm}^{-1}$  in 9:1  $\text{H}_2\text{O}:\text{MeCN}$ ; Figure S17). Under aerobic conditions in neat acetonitrile, formation of **2a** was limited to ~46% yield. To improve both the reaction efficiency and rate, solvent mixtures containing water were examined. Notably, increasing the proportion of water led to a marked enhancement in reactivity, with the yield of **2a** reaching up to 90% in a 9:1  $\text{H}_2\text{O}:\text{MeCN}$  mixture (Figures 4 and S27, Table S11).<sup>52-53, 55, 80</sup> Reaction rates were also significantly accelerated under aqueous conditions, with complete conversion achieved within 1.5 h at 70 °C (Figure S28, Tables S12 and S13). These results highlight the unusually mild nature of this aerobic C–H bond activation, which proceeds without an added external base, compared to typical aerobic C–H functionalization reactions that require higher temperatures and longer reaction times.<sup>24, 29, 31, 34-37, 49</sup>



**Figure 4.** Yield comparison of product **2a** and byproduct  $\text{H}_2\text{O}_2$  during the reaction of **1a** with  $\text{O}_2$  in two different  $\text{H}_2\text{O}:\text{MeCN}$  solvent mixture ratios.

To probe the stoichiometric role of  $\text{O}_2$  in this transformation, reactions of **1a** were conducted using varying equivalents of  $\text{O}_2$  (Figure S32). In 9:1  $\text{H}_2\text{O}:\text{MeCN}$ , exposure of 1 or 0.5



equivalents of O<sub>2</sub> afforded the C–H activated Pd<sup>III</sup> complex **2a** in 83% and 79% yield, respectively, whereas use of 0.25 equivalents of O<sub>2</sub> resulted in approximately 50% yield of **2a**. These observations indicate that O<sub>2</sub> functions as a two-electron oxidant in this system.<sup>81-83</sup> Consistent with this assignment, simultaneous formation of hydrogen peroxide was detected spectrophotometrically,<sup>84-86</sup> with the reaction of **1a** (1.05 mM) and excess O<sub>2</sub> in 9:1 H<sub>2</sub>O:MeCN producing **2a** in 90% yield along with H<sub>2</sub>O<sub>2</sub> in ~42% yield. In contrast, under otherwise identical conditions in neat acetonitrile, formation of H<sub>2</sub>O<sub>2</sub> was negligible (<3%), and the yield of **2a** remained limited to ~46%. These results suggest that while the initial C–H bond activation is accessible in both solvents, the subsequent C–H bond activation step is strongly suppressed in pure MeCN. As a consequence, the overall reaction in neat acetonitrile terminates after formation of approximately half an equivalent of the C–H activated Pd<sup>III</sup> complex. By comparison, under aqueous conditions, both the initial and subsequent C–H bond activation steps proceed, resulting in the formation of one equivalent of **2a** and half an equivalent of H<sub>2</sub>O<sub>2</sub> per equivalent of **1a**. The origin of this pronounced solvent dependence is addressed through computational analysis (vide infra). Under 9:1 H<sub>2</sub>O:MeCN conditions, the full time-course data (> 3 t<sub>1/2</sub>) were also analyzed by second-order global nonlinear fitting with explicit consideration of the overall reaction stoichiometry. The resulting rate constants at each temperature closely match those obtained from the corresponding initial rate analysis (see Supporting Information), confirming the validity of the second-order kinetic treatment.

To further probe the nature of the rate-determining step, an Eyring analysis was conducted under aqueous conditions over the temperature range of 20–70 °C (Figure S31). The resulting activation parameters ( $\Delta H^\ddagger = 16.7 \text{ kcal mol}^{-1}$  and  $\Delta S^\ddagger = -11.8 \text{ cal mol}^{-1} \text{ K}^{-1}$ ) correspond to a  $\Delta G^\ddagger$  of 20.2 kcal mol<sup>-1</sup> at 20 °C. The negative entropy of activation, together with the observed second-



order kinetics, is consistent with a bimolecular, associative transition state, in which O<sub>2</sub> and the Pd<sup>II</sup> complex interact during the rate-determining C–H bond activation step.<sup>87-91</sup> Based on these kinetic observations, we propose the following mechanism for the aerobic C–H bond activation of **1**.

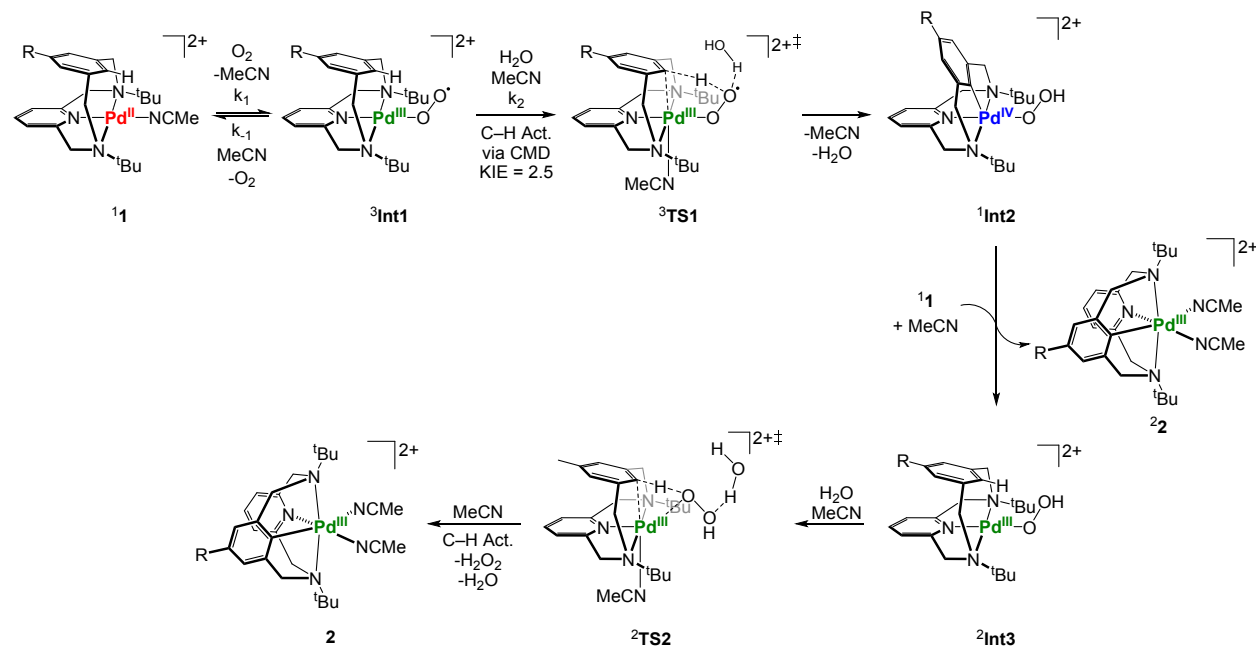
### Proposed mechanism and rate law for the aerobic oxidation of **1**

Based on our experimental observations and by analogy to acetate-assisted cyclopalladation reactions,<sup>92</sup> we propose a mechanism for the aerobic oxidation of **1** (Figure 5) under aqueous conditions. Oxidation of the Pd<sup>II</sup> complex **1** by O<sub>2</sub> generates a Pd<sup>III</sup>-superoxide intermediate (**Int1**), which is expected to form reversibly and be present in trace amount under the reaction conditions. The Pd<sup>III</sup>-superoxide species subsequently undergoes C–H bond activation via transition state **TS1**, which constitutes the rate-determining step of the reaction. The observed second-order kinetics, KIE, and Eyring analysis are all consistent with C–H bond activation being rate-limiting. The negative Hammett  $\rho$  value further supports an electrophilic-type transition state, consistent with a concerted C–H bond activation pathway. Following this step, a high-valent Pd<sup>IV</sup>-hydroperoxide intermediate (**Int2**) is formed, which undergoes rapid comproportionation and ligand exchange with another equivalent of **1** to generate the C–H activated product **2** and a Pd<sup>III</sup>-hydroperoxide species (**Int3**).<sup>52-53, 93-94</sup>

In the presence of water, the Pd<sup>III</sup>-hydroperoxide intermediate undergoes a subsequent, faster C–H bond activation to afford an additional equivalent of **2** with concomitant formation of hydrogen peroxide. Notably, this pathway is significantly suppressed in pure MeCN, accounting for the solvent-dependent product yields observed experimentally. To further evaluate the proposed mechanism, a rate law was derived using a steady-state treatment of <sup>3</sup>**Int1** (Scheme 1). The resulting expression predicts first-order dependence on both [**1**] and [O<sub>2</sub>], consistent with the

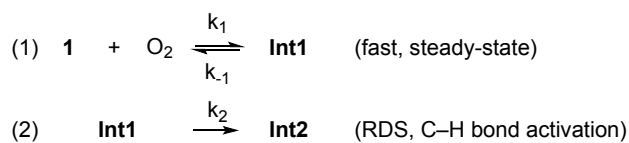


experimentally observed kinetic data.



**Figure 5.** Proposed mechanism for the aerobic oxidation of **1** under aqueous conditions.

**Scheme 1.** Proposed kinetic model for the aerobic oxidation of **1** analyzed using the steady-state approximation.



$$\text{rate} = \frac{k_1 k_2}{k_{-1} + k_2} [\mathbf{1}] [\text{O}_2]$$

While the experimental data are consistent with a CMD-like C–H bond activation pathway,



operating without an added external base, additional insight into the elementary steps was sought through computational studies.

### Computational investigation of C–H bond activation without an exogenous base

To validate the experimentally proposed CMD-like C–H bond activation mechanism operating without an added external base, density functional theory (DFT) calculations were performed (Figure 6). These calculations were designed to define the electronic structure of the oxygen-bound intermediates, identify the rate-determining step, and rationalize the experimentally observed solvent-dependent reactivity.

The reaction pathway begins with oxidation of the Pd<sup>II</sup> species **1a** to generate an oxygen-bound Pd intermediate, upon replacement of the coordinated acetonitrile with O<sub>2</sub>. Multiple electronic formulations and binding modes were evaluated computationally, including a singlet Pd<sup>III</sup>-superoxo species (<sup>1</sup>**Int6**, 35.7 kcal mol<sup>-1</sup>), a Pd<sup>IV</sup>-peroxo species (<sup>1</sup>**Int5**, 28.5 kcal mol<sup>-1</sup>; Figure S53), and the triplet Pd<sup>III</sup>-superoxo complex <sup>3</sup>**Int1**. Among these possibilities, the Pd<sup>III</sup>-superoxo complex <sup>3</sup>**Int1** was identified as the lowest-energy intermediate (11.9 kcal mol<sup>-1</sup>), lying 16.6 kcal mol<sup>-1</sup> below the corresponding Pd<sup>IV</sup>-peroxo species. These results indicate that the triplet Pd<sup>III</sup>-superoxo (<sup>3</sup>**Int1**) provides the most favorable electronic structure under the present reaction conditions.

The possibility of a binuclear Pd-oxygen intermediate species was also considered. Although the present calculations do not categorically exclude all possible binuclear pathways, our computational survey did not identify a binuclear oxygen-bound structure competitive in energy with the mononuclear Pd<sup>III</sup>-superoxo species <sup>3</sup>**Int1**. This computational assessment is also consistent with the experimentally observed first-order dependence on [Pd] under the examined conditions, which would not support a binuclear pathway involving association of two Pd centers



prior to or during the rate-limiting C–H activation step. Accordingly, the available kinetic and computational data are most consistent with assignment of **<sup>3</sup>Int1** as the initial Pd-oxygen intermediate in the proposed mechanism.

In the Pd<sup>III</sup>-superoxo complex **<sup>3</sup>Int1**, the distal oxygen atom of the superoxo ligand is positioned to engage the H<sub>ipso</sub> hydrogen, enabling a concerted C–H bond activation through transition state **<sup>3</sup>TS1** ( $\Delta G^\ddagger = 19.6 \text{ kcal mol}^{-1}$ ). The geometry and electronic structure of **<sup>3</sup>TS1** are characteristic of a CMD-like process, in which the superoxo ligand functions as an internal base to abstract the proton concomitant with Pd–C bond formation. Hydrogen bonding between a water molecule and the distal oxygen atom of the superoxo ligand in **<sup>3</sup>TS1** facilitates the initial C–H activation, resulting in a lower activation free energy compared to non-hydrogen bonded transition state **<sup>3</sup>TS4** ( $25.9 \text{ kcal mol}^{-1}$ , Figure S53). Passage through this transition state leads directly to formation of a high-valent Pd<sup>IV</sup>-hydroperoxo intermediate (**<sup>1</sup>Int2**).<sup>52-53, 55-56, 95</sup> Notably, the computed activation barrier for this step closely matches the experimentally derived barrier from Eyring analysis ( $\Delta G^\ddagger_{\text{obs}} = 20.2 \text{ kcal mol}^{-1}$  at 20 °C), confirming that the initial C–H bond activation constitutes the rate-determining step of the overall reaction.

Following the first C–H bond activation, ligand exchange and facile comproportionation between the Pd<sup>IV</sup>-hydroperoxo intermediate **<sup>1</sup>Int2** and an additional equivalent of the Pd<sup>II</sup> reactant **1a** afford the C–H activated Pd<sup>III</sup> product **2a** along with a Pd<sup>III</sup>-hydroperoxide species (**<sup>2</sup>Int3**). While this step is energetically accessible, further C–H bond activation from **<sup>2</sup>Int3** is highly sensitive to solvent effects.

In the presence of water, the Pd<sup>III</sup>-hydroperoxide intermediate **<sup>2</sup>Int3** undergoes a subsequent C–H bond activation via transition state **<sup>2</sup>TS2** ( $\Delta G^\ddagger = 13.2 \text{ kcal mol}^{-1}$ ), yielding an additional equivalent of product **2a** with concomitant formation of hydrogen peroxide. In **<sup>2</sup>TS2**, hydrogen

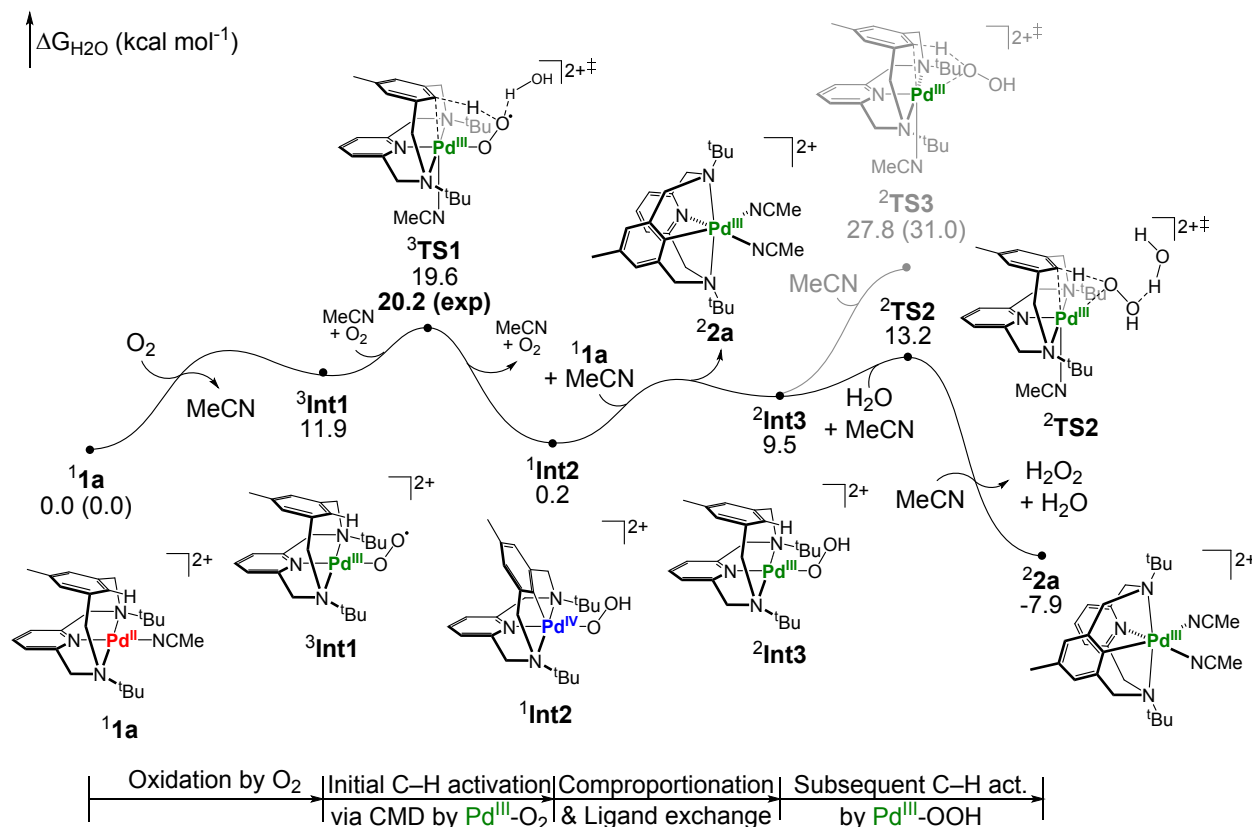


bonding between a water molecule and the distal oxygen atom of the hydroperoxide ligand significantly stabilizes the transition state, resulting in a substantial reduction of the activation barrier. By contrast, the corresponding water-free transition state  ${}^2\text{TS3}$  exhibits a much higher barrier ( $\Delta G^\ddagger = 27.8 \text{ kcal mol}^{-1}$ ), and the barrier increases further under pure MeCN conditions ( $\Delta G^\ddagger = 31.0 \text{ kcal mol}^{-1}$ ). The pronounced energetic difference ( $\Delta\Delta G^\ddagger = 14.6 \text{ kcal mol}^{-1}$ ) accounts for the experimentally observed solvent dependence, wherein significantly higher yields of **2a** are obtained under aqueous conditions (9:1 H<sub>2</sub>O:MeCN, 90%) compared to pure MeCN (46%), where the subsequent C–H bond activation is largely suppressed.

The stabilizing role of hydrogen bonding in facilitating hydroperoxide-mediated reactivity is consistent with prior observations in related systems, where interaction with the distal oxygen of the hydroperoxide ligand has been shown to promote bond activation.<sup>96</sup> To assess whether water could alternatively function as a proton shuttle during the subsequent C–H bond activation, additional pathways involving explicit proton transfer through water were evaluated (Figure S53).<sup>97</sup> However, the computed activation barriers for these pathways ( $\Delta G^\ddagger = 28.6 \text{ kcal mol}^{-1}$  for  ${}^2\text{TS8}$  and  ${}^2\text{TS9}$ ) were comparable to that of the water-free transition state  ${}^2\text{TS3}$ , indicating that proton shuttling does not significantly lower the barrier in this system.

Overall, the computational results are consistent with the experimental observations and support an aerobic C–H bond activation mechanism in which a Pd-O<sub>2</sub> species serves as a proton acceptor, without the need for an added exogenous base. The calculations establish that the CMD-like C–H bond activation by a Pd<sup>III</sup>-superoxo species constitutes the rate-determining step, while solvent-enabled hydrogen bonding plays a decisive role in lowering the barrier for C–H bond activations. These insights collectively rationalize the observed kinetics, solvent effects, and product distributions under aerobic conditions.





**Figure 6.** Computed energy profile for the aerobic C–H bond activation of **1a** promoted by  $O_2$  to generate the  $Pd^{III}$  product **2a** under aqueous conditions. Gibbs energies were calculated using the solvent model density (SMD) method in water, with selected energies for **1a** and **2TS3** in MeCN shown in parentheses. The experimentally measured  $\Delta G^\ddagger$  at 293 K for the overall C–H bond activation process is shown in bold under the calculated Gibbs energies for **3TS1**.

## Conclusions

Herein, we report an aerobic C–H bond activation without an exogenous base mediated by the  $Pd$  complex  $[(P^R N_3 CH)Pd^{II}(MeCN)](BF_4)_2$ , **1**, under aqueous conditions at room temperature, affording the  $Pd^{III}$  product  $[(P^R N_3 C)Pd^{III}(MeCN)_2](BF_4)_2$ , **2**. Combined experimental and



computational data support that a CMD-like C–H bond activation constitutes the rate-determining step, in which a proposed Pd–superoxide species functionally acts as the base in a traditional CMD process. Water plays a critical role in lowering the activation barrier, enabling near-quantitative product formation, while O<sub>2</sub> acts as both oxidant and proton acceptor, producing H<sub>2</sub>O<sub>2</sub> as the sole byproduct. A slight increase in reaction temperature substantially shortens the reaction time to under two hours, highlighting the practical viability of O<sub>2</sub> as a green oxidant for C–H bond activation under aqueous conditions.

Overall, this study establishes a mechanistically distinct and sustainable strategy for aerobic C–H bond activation that proceeds at a Pd center without an added external base. These findings provide fundamental insight into the design of aerobic oxidation processes under mild and environmentally benign conditions and further expand the scope of high-valent palladium chemistry.

## ASSOCIATED CONTENT

### Data availability

Synthetic details, spectroscopic characterization, mechanistic and kinetic studies, crystallographic data, and computational details are available in the Supporting Information. The deposition numbers CCDC 2331324 (for **1a**), 2331325 (for **1ab**), and 2331326 (for **2a**) contain the supplementary crystallographic data for this paper.

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### Author contributions

D.Y.B. and L.M.M. conceptualized and designed the project. D.Y.B. and L.M.M. designed the experiments and computations. Experimental work was conducted by D.Y.B. and N.P.R., with N.P.R. contributing to the initial investigation. D.Y.B. and L.M.M. wrote the manuscript with input from all authors. L.M.M. directed the project.

### Conflicts of interest

The authors have no conflicts to declare.

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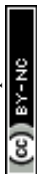
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## Data Availability Statement

Synthetic procedures, spectroscopic data, mechanistic and kinetic studies, crystallographic details, and computational results are available in the Supporting Information. The deposition numbers CCDC 2331324 (for **1a**), 2331325 (for **1ab**), and 2331326 (for **2a**) at the Cambridge Crystallographic Data Centre (CCDC) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the CCDC (<https://www.ccdc.cam.ac.uk/>).

