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Evidence of a Wheland Intermediate in Carboxylate-Assisted C(sp²)–H Activation by Pd(IV) Active Catalyst Species Studied via DFT Calculations

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Abstract: Evidence of a Wheland intermediate in carboxylate-assisted C–H activation was found using DFT calculations when the Pd(IV) catalyst species was postulated as the active catalyst species (ACS). In order to delineate the reaction mechanism of Pd-catalyzed bisarylation of 3-alkylbenzofuran, five hypothetical catalyst species, [Pd(OAc)(PMe₃)(Ph)] (I), [Pd(OAc)₂] (II), [Pd(OAc)₂(PMe₃)] (III), [Pd(OAc)₂(Ph)]⁺ (IV) and [Pd(OAc)₂(PMe₃)(Ph)]⁺ (V) were tested as potential ACS candidates. The catalyst species I, previously reported as an ACS in the context of ambiphilic metal–ligand assistance or a concerted metalation-deprotonation mechanism, was unsuccessful, with maximum activation barriers ($\Delta G^\ddagger_{\text{max}}$) for the C(sp²)–H and C(sp³)–H activations of 33.3 and 51.4 kcal/mol, respectively. The $\Delta G^\ddagger_{\text{max}}$ values for the C(sp²)–H and C(sp³)–H activations of II–V were 23.8/28.7, 32.0/49.6, 10.9/10.9, and 36.0/36.0 kcal/mol, respectively, indicating that ACS is likely IV. This catalyst species forms an intermediate state (IV_1) before proceeding to the transition state (IV_TS1,2) for C(sp²)–H activation, in which C(2) atom of 3-methylbenzofuran has a substantial σ -character. The degree of σ -character of the IV_1 state was further evaluated quantitatively in terms of geometric parameters, partial charge distribution, and activation strain analysis. The analysis results support the existence of a Wheland intermediate, which has long been recognized as the manifestation of the electrophilic aromatic substitution mechanism yet never been identified computationally.

Keywords: C–H activation; Wheland intermediate; electrophilic substitution; CMD; AMLA; carboxylate-assisted; active catalyst species; Pd(IV)



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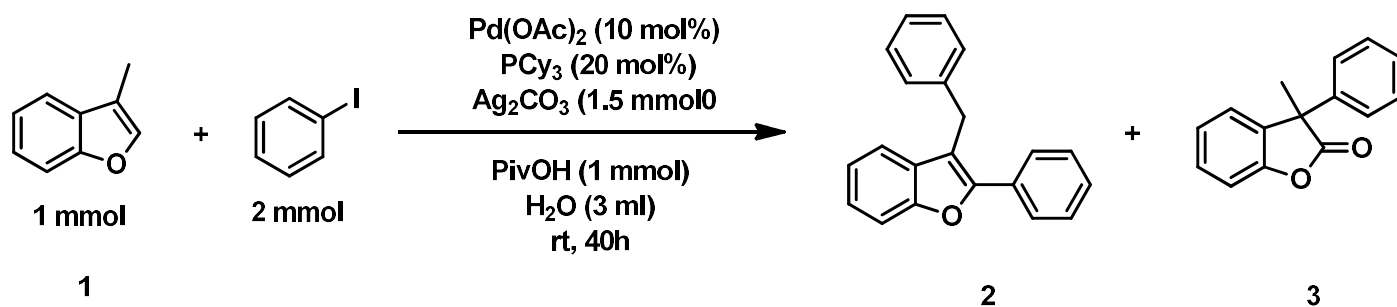


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1. Introduction

Transition-metal-catalyzed direct C–H bond activation has emerged as a crucial topic in modern organometallic chemistry due to its potential for the catalytic functionalization of naturally abundant hydrocarbons [1–9]. The ability to activate C–H bonds without the need for prefunctionalization steps offers a more sustainable and atom-economical synthetic route to valuable chemicals and materials. Moreover, it offers a new strategy to access complex molecular architectures that are difficult to prepare using traditional synthetic methods. The elucidation of the underlying mechanisms of C–H bond activation reactions is essential for advancing this field and developing more efficient and selective catalysts. The mechanism of transition-metal-catalyzed C–H activation processes at the early stage of its development involves (i) oxidative addition with electron-rich late transition metals, (ii) σ -bond metathesis with early transition metals, (iii) 1,2-addition with both early and late transition metals, and (iv) electrophilic aromatic substitution (S_EAr) mainly with late transition metals [3,8,10–13]. However, recent mechanistic studies have suggested that the major interaction between the transition-metal catalyst and substrate resides within the continuum of electrophilic, ambiphilic, and nucleophilic interactions [8,14,15].

Recently, Chung and coworkers reported the Pd-catalyzed bisarylation of 3-alkylbenzofuran (Scheme 1) [16]. Tandem $C(sp^2)$ -H and $C(sp^3)$ -H activations occurred even with only one equivalent of phenyl iodide in this reaction. This reaction utilized a catalyst system comprising a transition metal precursor complex aided by bifunctional ligands bearing a Lewis-basic heteroatom. The researchers employed $[Pd(OAc)_2]$ as a catalyst precursor and pivalate as a bifunctional ligand. These conditions have been commonly known as “carboxylate-assisted C–H activation”, which has gained widespread popularity in recent years due to its ease of C–H activation [8,17–19].



Scheme 1. Pd-catalyzed bisarylation of 3-alkylbenzofurans to 3-arylalkyl-2-arylbenzofurans.

The mechanism of this reaction has been under intense investigation and a comprehensive summary of the scientific efforts has been provided [8,12,18]. Initially, carboxylate-assisted C–H activation was considered to be S_EAr , with the Wheland intermediate being prevalent [10]. However, despite extensive efforts, no convincing computational evidence for S_EAr has been reported [18]. Recent mechanistic investigations have instead conceptualized these reactions in terms of “ambiphilic metal–ligand assistance” (AMLA) [20,21] or “concerted metalation-deprotonation” (CMD) [22–24], with the former emphasizing the presence of an agostic intermediate prior to the main C–H activation. These concepts were validated by computational studies [21,24]. In this context, the term electrophilic CMD (eCMD) has been introduced recently to describe cases in which the mechanism falls between the CMD and S_EAr [25].

In Chung and coworker’s report, there were a couple of important experimental results that provided insights to elucidate the reaction mechanism [16]: (i) The reaction proceeds at room temperature, implying that the energetic span ($\Delta G^\ddagger_{span}$) [26–29] for the entire reaction pathway is small. (ii) The kinetic isotope effect (KIE) experiment (KIE values for $k_1/k_{1-D} = 1.2$ and $k_1/k_{1-CD_3} = 1.1$) indicated that the C–H bond cleavage event, whether $C(sp^2)$ -H or $C(sp^3)$ -H, is not rate-determining.

Based on these experimental clues, we commenced our computational work to understand the reaction mechanism of this peculiar results, assuming that the reaction mechanism was based on AMLA or CMD. We chose the structure of the active catalyst species (ACS) as $[Pd(OAc)(PMe_3)(Ph)]$ (I) inspired by Fagnou’s work [23], given the similarity of the reaction conditions between the two groups. The structural motifs of the key transition states for the C–H bond cleavage processes were adopted from related computational studies [23,24,30]. While the details of this computational study will be described in the later part of this manuscript, only the calculation results obtained with I as ACS showed that the $\Delta G^\ddagger$ values for the $C(sp^2)$ -H and $C(sp^3)$ -H activations were 33.3 and 51.4 kcal/mol, respectively, from the initial state. These calculation results appeared to be inconsistent with the experimental results, according to which the reaction proceeded even at 25 °C, implying that other species could work as an ACS.

The identification of the correct ACS and the formation of an appropriate catalyst–substrate adduct conformation are crucial prerequisites in computational studies aimed at understanding the mechanism of transition-metal-catalyzed organic transformations [12,18]. The transient nature of reactive intermediates and transition states as well as the structural changes that ACS undergoes during the catalytic cycle make it challenging to obtain

experimental structural information [18]. Therefore, computational studies, which are not limited by these restrictions, have therefore become a valuable research tool in the field of homogeneous catalysis. Advances in density functional theory (DFT) calculations have significantly impacted this area of research, leading to a growing reliance on DFT calculations in investigations of catalytic mechanisms [31–33].

In order to identify the species that acts as the ACS in the above mentioned reaction, we considered a series of Pd complexes as potential candidates for DFT calculations. During the investigation of the reaction mechanism in these hypothetical complexes, we found that $[\text{Pd}(\text{OAc})_2(\text{Ph})]^+$ (IV) could serve as a competent ACS of the reaction, even in the absence of a phosphine ligand. Further analysis of the $\text{C}(\text{sp}^2)\text{--H}$ activation pathway revealed that it proceeds via a Wheland intermediate, suggesting that the reaction mechanism may be a $\text{S}_{\text{E}}\text{Ar}$ reaction. The results of this computational study are presented in this report.

2. Results and Discussion

When 3-methylbenzofuran approached I (1), intermediate I_1 formed, likely due to the electron-rich nature of the heteroarene substrate (Figure 1). This process was found to be substantially endergonic by 20.7 kcal/mol with an activation barrier of 21.4 kcal/mol. In the I_1 state, the substrate was positioned trans to the phosphine ligand, with Pd–C(2) and Pd–C(3) distances of 2.499 and 2.830 Å, respectively (Figure 2a). Being not perfect, the interaction mode between the ACS and the substrate was an η^2 π -bond. The distances between C(2)–H and Pd–H were found to be 1.084 and 2.609 Å, respectively, indicating that the C(2)–H bond was not polarized and the agostic interaction between Pd and H atoms was not present [21]. A more detailed analysis of the structures of the intermediate and subsequent transition states will be provided in the later part of this manuscript.

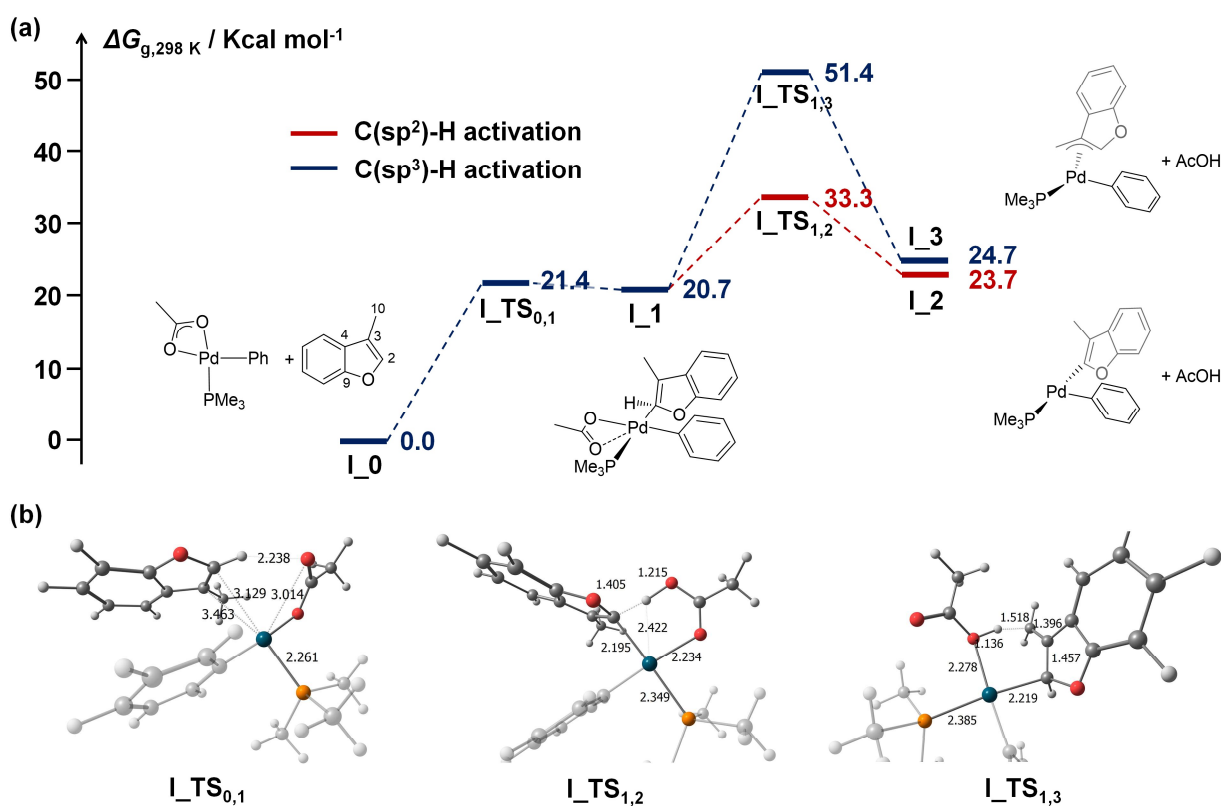


Figure 1. (a) Free energy reaction profile for C(sp²)-H (red) and C(sp³)-H (blue) activation by I. Numbers are ΔG in water at 298 °C (energies in kcal/mol). (b) Optimized geometries of transition states with selected bond lengths (Å). The phenyl and trimethylphosphine groups are drawn translucent for clarity.

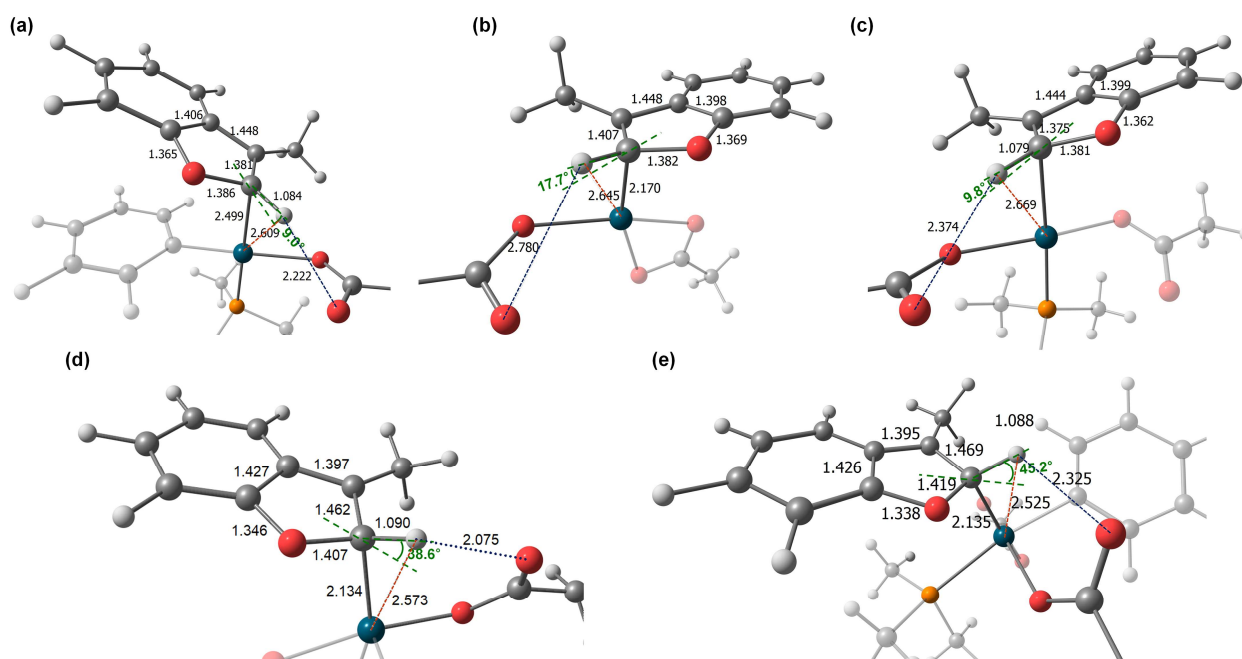


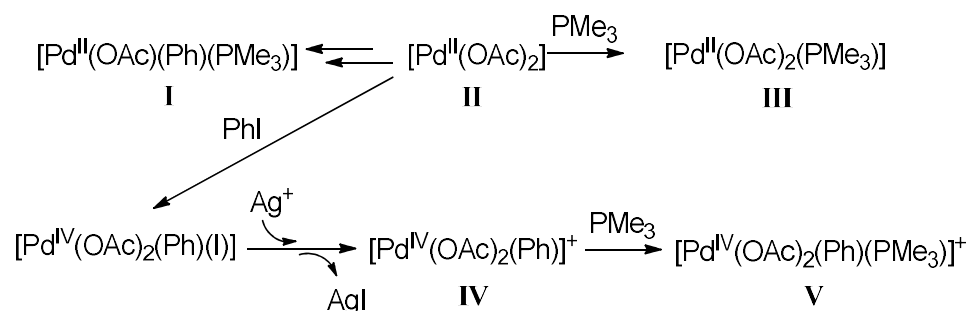
Figure 2. Optimized geometries of intermediate states prior to the C–H bond cleavage: (a) **I**₁ (Figure 1), (b) **II**₁ (Figure 3), (c) **III**₁ (Figure 4), (d) **IV**₁ (Figure 5), and (e) **V**₁ (Figure 6). Interactions between acetate oxygen atom and C(*sp*²)–H atoms are shown as blue dotted lines. Pd–H interactions are shown as orange dotted lines. Deviation angles (α) defined in the figure of Table 2 are displayed in green. Note that (a–c) are neutral and (d,e) are +1 cationic.

The intermediate, **I**₁, was observed to diverge into two distinct transition states, **I**_{TS1,2} and **I**_{TS1,3}, that corresponded to the C(*sp*²)–H and C(*sp*³)–H activation pathways, respectively. The structures of these transition states were obtained through potential scans by rotating the Pd–C(2) bond in clockwise and counterclockwise directions, leading to the formation of six-membered-ring structural motifs (Figure 1b). The constituting atoms in these six-membered rings differed between the two transition states, with the former featuring Pd–C(2)–H–O–C– κ^1 –O and the latter having Pd–C(2)–C(3)–C(10)–H– κ^1 –O. Notably, the C(10)–H bond in **I**_{TS1,3} did not directly interact with the Pd metal and was instead facilitated by the κ^1 –O atom of the acetate ligand, which has been characterized as allylic C–H activation [34–37]. Meanwhile, C(*sp*²)–H cleavage was supported by the displaced carbonyl oxygen. The consideration of a four-membered-ring structural motif involving Pd, C(2), H, and κ^1 –O for C(*sp*²)–H activation was also evaluated. However, it was discarded due to its significantly higher free energy compared to its six-membered-ring analog.

The activation energy ($\Delta G^\ddagger$) required for the C(*sp*²)–H and C(*sp*³)–H activation from the intermediate state **I**₁ was calculated to be 12.6 and 30.7 kcal/mol, respectively. The differences in energies between the transition state (TS) and the initial state (**I**₀), in which **I** and **1** were isolated, were thus the maximum free energy barriers ($\Delta G^\ddagger_{\text{max}}$) [38] for these processes, which were determined to be 33.3 and 51.4 kcal/mol for C(*sp*²)–H and C(*sp*³)–H activations, respectively. The free energies of the product states, **I**₂ and **I**₃, were calculated to be 23.7 and 24.7 kcal/mol, respectively, relative to the **I**₀ state, indicating an overall endergonic nature of these reactions. These results were not in agreement with the experimental observation, as the reaction proceeded even at 25 °C, suggesting the possibility of the existence of another species acting as the ACS. Careful exploration to identify the ACS is thus necessary before further elucidation of the entire reaction mechanism.

As mentioned in the introduction, we considered four additional model complexes as potential candidates for the ACS. The structures of these complexes were speculated based

on their generation routes, as outlined in Scheme 2. The starting point was the catalyst precursor $[\text{Pd}(\text{OAc})_2]$ (**II**), which could be transformed into $[\text{Pd}(\text{OAc})_2(\text{PCy}_3)]$ upon the addition of PCy_3 . The formation of $[\text{Pd}(\text{OAc})_2(\text{Ph})]^+$ (**IV**) could be achieved through the oxidative addition of phenyl iodide to **II**, followed by the dehalogenation by Ag^+ . The addition of PCy_3 to **IV** would result in the formation of $[\text{Pd}(\text{OAc})_2(\text{Ph})(\text{PCy}_3)]^+$. In order to reduce computational costs, PCy_3 was replaced with PMe_3 in the model complex, resulting in the establishment of $[\text{Pd}(\text{OAc})_2(\text{PMe}_3)]$ (**III**) and $[\text{Pd}(\text{OAc})_2(\text{Ph})(\text{PMe}_3)]^+$ (**V**) as representative model complexes instead of $[\text{Pd}(\text{OAc})_2(\text{PCy}_3)]$ and $[\text{Pd}(\text{OAc})_2(\text{Ph})(\text{PCy}_3)]^+$.



Scheme 2. Generation of ACS candidates I–V.

The initial computational investigation of the carboxylate-assisted C–H activation was reported by Sakaki et al., involving benzene and methane as model substrates for $\text{C}(\text{sp}^2)\text{--H}$ and $\text{C}(\text{sp}^3)\text{--H}$ activation, respectively, and $[\text{M}(\kappa^2\text{--O}_2\text{CH})_2]$ ($\text{M} = \text{Pd}, \text{Pt}$) as the ACS [39]. According to this mechanism, the activation process involves the formation of an intermediate state where a formate ligand is displaced from the κ^2 to κ^1 mode, followed by heterolytic cleavage of the C–H bond. In line with this scenario, we performed calculations on the **II** ACS (Figure 3).

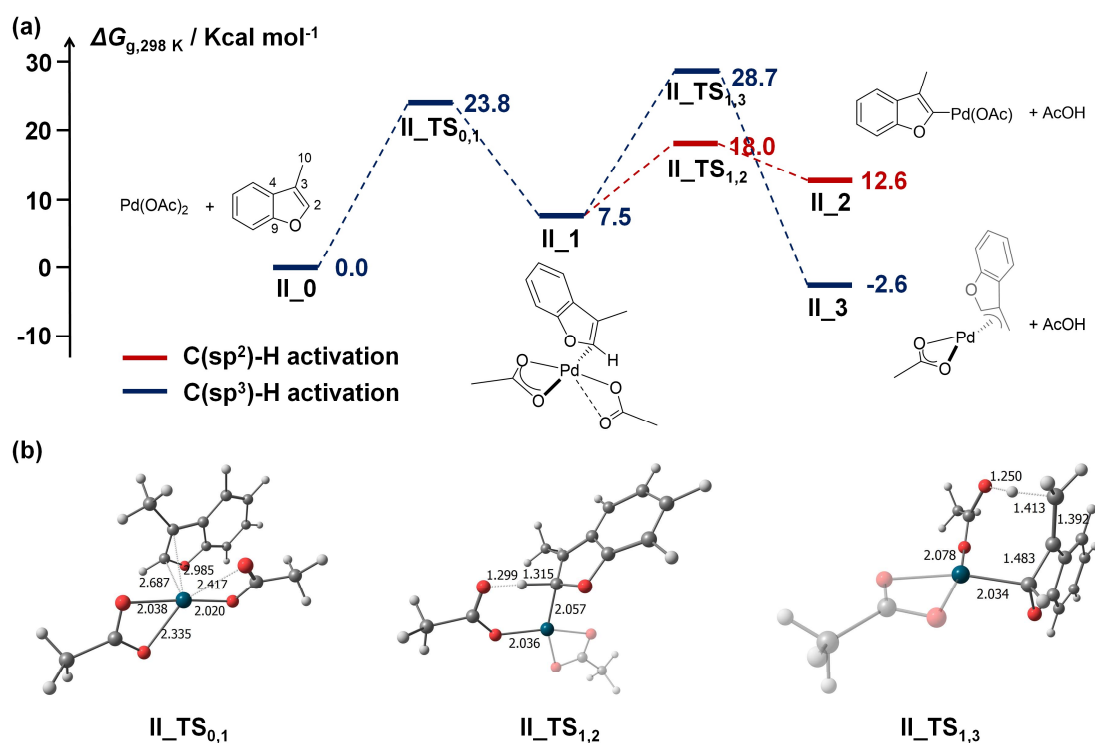


Figure 3. (a) Free energy reaction profile for $\text{C}(\text{sp}^2)\text{--H}$ (red) and $\text{C}(\text{sp}^3)\text{--H}$ (blue) activation by **II**. Numbers are ΔG in water at 298 °C (energies in kcal/mol). (b) Optimized geometries of transition states with selected bond lengths (Å). The spectator acetate group is drawn translucent for clarity.

The intermediate state **II**_1, in which the C(2) atom of **1** occupies one coordination site of the pseudo-square planar geometry of **II**, was located. This process was endergonic by 7.5 kcal/mol and required the κ^2 -to- κ^1 displacement of one carboxylate ligand whose $\Delta G^\ddagger$ was 23.8 kcal/mol. The C(2)–H and Pd–H distances of **II**_1 were 1.078 and 2.645 Å, respectively, indicating a lack of agostic character (Figure 2b) [21]. The structural motif of the transition state for the C–H activation was similar to that obtained for **I** and featured a characteristic six-membered-ring geometry. However, a different transition state structure was obtained for C(sp^3)–H activation compared to that of **I**. From the **II**_1 structural configuration, a clockwise rotation of 3-methylbenzofuran around the Pd–C(2) bond facilitates an interaction between the displaced oxygen atom of the acetate ligand and the hydrogen atom of the methyl group. Subsequent potential scan by constricting the distance between these two entities led to the location of a transition state suitable for C(sp^3)–H activation. Notably, this transition state structural motif forms an unusual eight-membered-ring configuration comprising Pd–C(2)–C(3)–C(10)–H–O–C– κ^1 –O atoms. An alternative six-membered-ring transition state structure consisting of Pd–C(2)–C(3)–C(10)–H– κ^1 –O atoms was also obtained for C(sp^3)–H activation. However, this transition state exhibited an energy that was 5.8 kcal/mol higher than that of the eight-membered-ring counterpart. In spite of the revelation that an eight-membered-ring transition state geometry possesses a lower activation energy than the conventional six-membered-ring configuration, C(sp^3)–H activation still necessitates a notably higher activation energy than C(sp^2)–H activation, similar to the case of **I**. The $\Delta G^\ddagger$ values for the heterolytic cleavages of the C(sp^2)–H and C(sp^3)–H bonds from the **II**_1 state were 10.5 and 27 kcal/mol, respectively. As a result, the C(sp^2)–H activation was endergonic by 12.6 kcal/mol, while the C(sp^3)–H activation was mildly exergonic by –2.6 kcal/mol from the **II**_0 initial state. Notably, given the fact that the energy of **II**_TS_{1,2} is lower than that of **II**_TS_{0,1}, the overall free energy barrier governing the formation of **II**_2 is determined by **II**_TS_{0,1}, whereas that governing the formation of **II**_3 is dictated by **II**_TS_{1,3}, with the values of 23.8 and 28.7 kcal/mol, respectively.

We next examined the C–H activation pathway using an active catalytic species in which phosphine is bound to [Pd(OAc)₂]. The approach of **1** towards the metal center of **III** necessitated the displacement of oxygen atom of the κ^2 -carboxylate ligand. The $\Delta G^\ddagger$ of this process was in a similar level with the case **II** (21.7 kcal/mol). However, the energy of the **III**_1 state was 16.2 kcal/mol higher than that of **III**_0 indicating that this process is highly endergonic (Figure 4). The resulting **III**_1 state showed no agostic character between Pd and H atoms, as revealed by the C(2)–H and Pd–H distances of 1.079 and 2.669 Å (Figure 2c) [21]. The following C(sp^2)–H activation required 16.8 kcal/mol of $\Delta G^\ddagger$ from the **III**_1 state. This resulted in a combined $\Delta G^\ddagger$ of 32.0 kcal/mol from the **III**_0 state. For the C(sp^3)–H activation process, the $\Delta G^\ddagger$ was 34.4 kcal/mol, which was much greater than that of C(sp^2)–H activation, even if we considered the eight-membered-ring transition state geometry. The combined $\Delta G^\ddagger$ was 49.6 kcal/mol from the **III**_0 state. As a consequence of the significant stabilization of the **III**_0 state by 24.2 kcal/mol, the overall free energy barriers for C(sp^2)–H and C(sp^3)–H activation processes were determined to be 7.8 and 25.4 kcal/mol, respectively. However, the cumulative activation energies from the energy level of the **III**_0 state were found to be 32 and 49.6 kcal/mol, respectively. Moreover, the C(sp^2)–H activation was endergonic by 31.7 kcal/mol from the **III**_0 initial state. These results suggest that the ACS **III** confers no clear advantage over the ACS **II**.

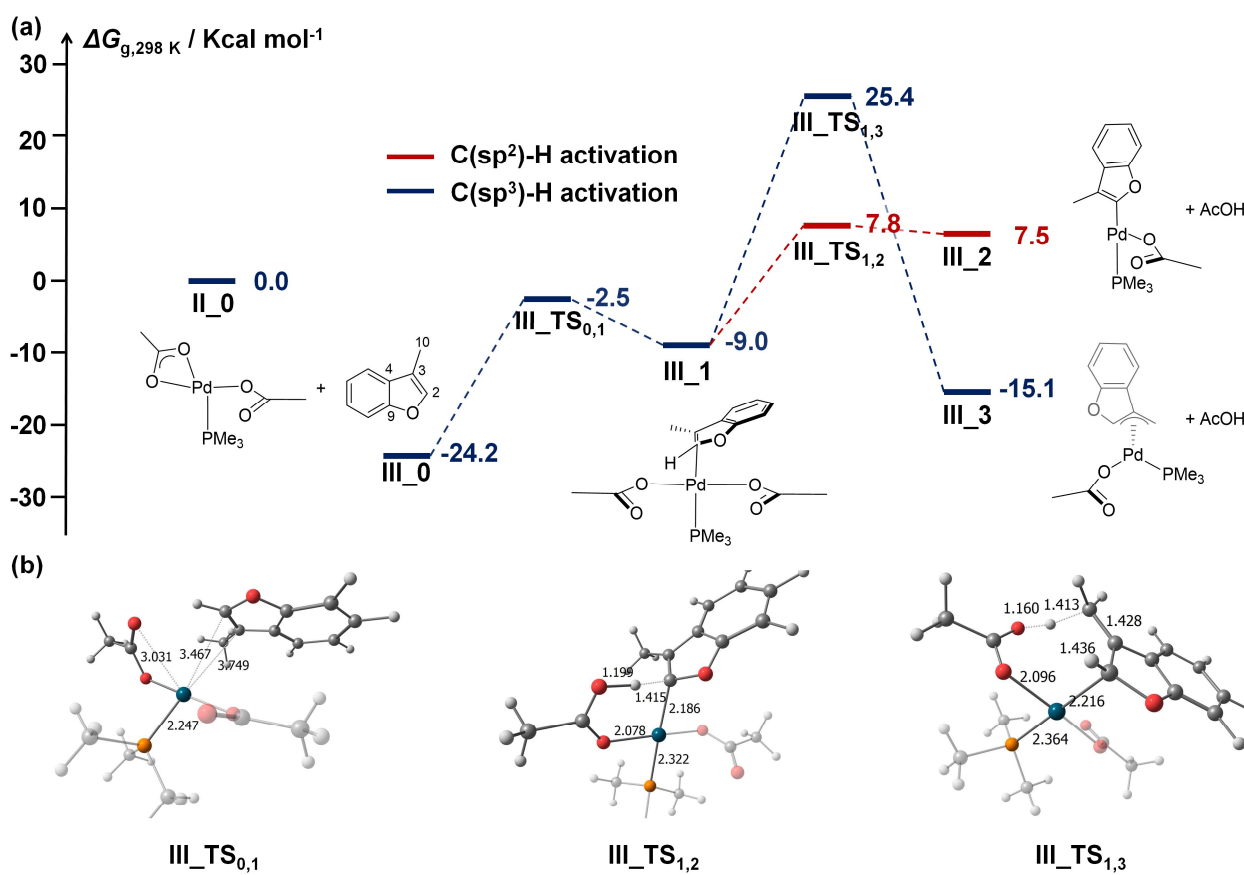


Figure 4. (a) Free energy reaction profile for C(sp²)-H (red) and C(sp³)-H (blue) activation by III. Numbers are ΔG in water at 298 °C (energies in kcal/mol). (b) Optimized geometries of transition states with selected bond lengths (Å). The spectator acetate and trimethylphosphine groups are drawn translucent for clarity.

We next considered the Pd(IV) catalyst species. Research on Pd(IV)-catalyzed C-H activation has recently become intense [19,40–44]. The presence of transient reactive Pd(IV) intermediate was detected by electrospray ionization tandem mass spectrometry [45]. Theoretical calculation results that support Pd(IV) species have been reported [46]. Additionally, the formation of 3,3'-dimethyl-[2,3'-bibenzofuran]-2'-(3'H)-one, which resembles **3** (Scheme 1) in terms of the benzofuranone structural motif, was confirmed by using an intentionally prepared Pd(IV) catalyst species [47]. Based on this information, we constructed complexes **IV** and **V** as potential models for ACS. The generation pathway of catalytic species **IV** and **V** has been postulated and depicted in Figure S1. The Gibbs free energies of **IV** and **V**, as calculated from the zero value of [Pd(OAc)₂] precursor state, are 6.6 and −14.9 kcal/mol, respectively. The $\Delta G^\ddagger_{\text{max}}$ value during the oxidative addition of phenyl iodide to the Pd metal center was found to be 34.6 kcal/mol. It is important to note that this oxidative addition pathway is hypothetical, and thus the $\Delta G^\ddagger_{\text{max}}$ value for the generation of **IV** is only an initial estimate. It is probable that a more efficient route may be present, which is our current research interest. Despite this, the calculated Gibbs free energies of **IV** and **V** are plausible, and it is appropriate to compare all energy levels of reaction pathways conducted by **IV** and **V** based on the energy level of the [Pd(OAc)₂] precursor state.

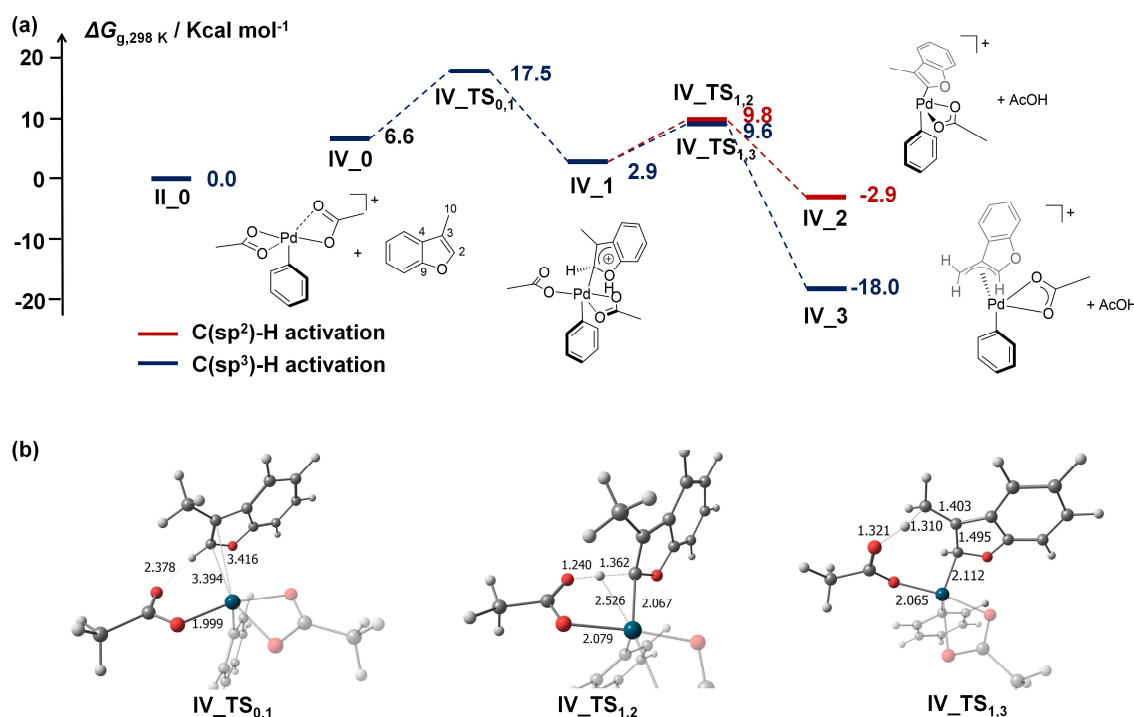


Figure 5. (a) Free energy reaction profile for C(sp²)-H (red) and C(sp³)-H (blue) activation by IV. Numbers are ΔG in water at 298 °C (energies in kcal/mol). (b) Optimized geometries of transition states with selected bond lengths (Å). The spectator acetate and phenyl groups are drawn translucent for clarity.

Upon substrate addition with its long axis orthogonal to the z-axis of IV, when the axis containing the phenyl group is set as the z-axis, the equatorial coordination site of IV, which was left vacant due to the elimination of the iodide ligand (as seen in Figure S1), was reoccupied by the incoming substrate forming an intermediate state IV_1. It is noteworthy to focus on the structure of IV. The distances between the two oxygen atoms of the acetate ligand on the *xy* plane and Pd are 1.960 and 2.120 Å, respectively, indicating that they are two κ^2 -O atoms. However, those on the *xz* plane and Pd are 1.975 and 2.607 Å, respectively, suggesting that one oxygen atom is clearly displaced from Pd to some extent. This oxygen atom weakly binds to Pd and can readily depart from its position upon substrate approach, placing itself in proximity to the C(2) hydrogen of 3-methylbenzofuran in the IV_1 state. As a result, the formation process of IV_1 differs significantly from the preceding three cases. While the preceding three processes were all endergonic and required more than 20 kcal/mol of activation barrier, this process is not only exergonic by 3.7 kcal/mol, but also has an activation energy of only 10.9 kcal/mol, which is much smoother than the previous processes. Additionally, both C(sp²)-H and C(sp³)-H activations proceed smoothly from IV_1. The geometry of IV_1 is inherently susceptible to C(sp²)-H activation, and rotating the κ^1 -OAc group counterclockwise around the Pd-O bond by approximately 110 degrees leads to the geometry of IV_TS_{1,3}, in which the characteristic eight-membered-ring structural motif is maintained, without disrupting the position of 3-methylbenzofuran. Consequently, the activation energies required to reach IV_TS_{1,2} or IV_TS_{1,3} from IV_1 are only 6.9 and 6.7 kcal/mol, respectively, and the energies of the resulting C(sp²)-H and C(sp³)-H activation product states are also significantly more stable, by 5.8 and 20.9 kcal/mol, respectively, than that of the IV_1 state. The energetic profiles for C(sp²)-H and C(sp³)-H activations exhibit a cascade-type behavior, with final Gibbs free energies of -2.9 and -18.0 kcal/mol, respectively. These results indicate that both C(sp²)-H and C(sp³)-H activation processes mediated by ACS IV are kinetically and thermodynamically favorable (Figure 5a).

Similar to the case of **III**, the addition of phosphine ligand to **IV** stabilized its energy significantly, which made the state energy of **V_0** -14.9 kcal/mol. Since all six coordination sites around the Pd metal were occupied, the addition of 3-methylbenzofuran to the metal center required a substantial $\Delta G^\ddagger$ of 36.0 kcal/mol. Not surprisingly, this process was found to be endergonic by 24.3 kcal/mol. The incoming substrate displaced one κ^2 -O atom of the acetate ligand and occupied one equatorial position of the Pd coordination sphere. In **V_1** state, the displaced oxygen atom positioned in proximity to the C(2) hydrogen of 3-methylbenzofuran with O–H distance of 2.325 Å ready for the next C(sp^2)–H activation. The subsequent C(sp^2)–H cleavage process occurred exergonically by 18.4 kcal/mol with a $\Delta G^\ddagger$ of 0.6 kcal/mol through the conventional six-membered-ring structural motif.

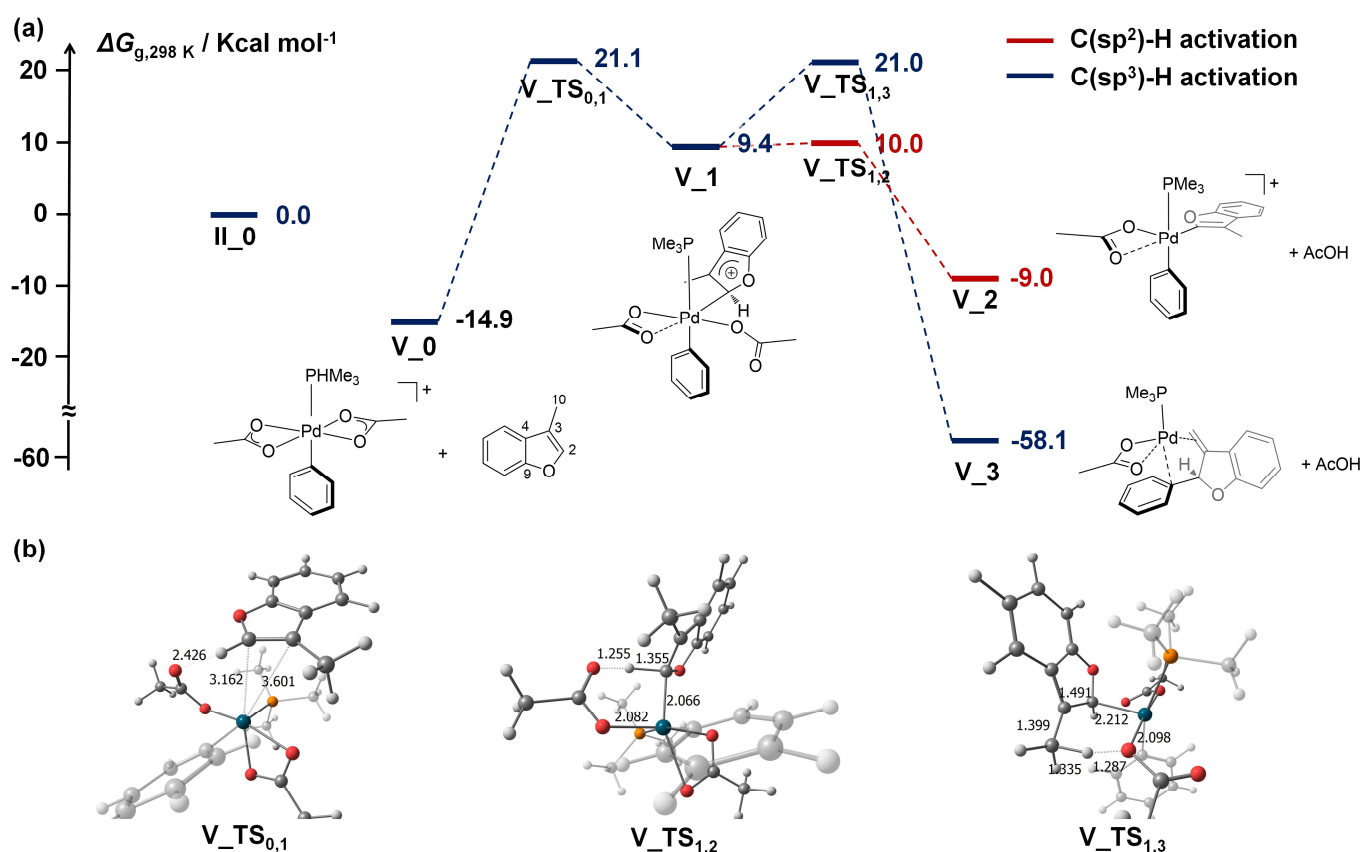


Figure 6. (a) Free energy reaction profile for C(sp^2)–H (red) and C(sp^3)–H (blue) activation by **V**. Numbers are ΔG in water at 298 °C (energies in kcal/mol). (b) Optimized geometries of transition states with selected bond lengths (Å). The phenyl and trimethylphosphine groups are drawn translucent for clarity.

In contrast to ACS **II–IV**, the C(sp^3)–H cleavage process by **V** did not proceed through the eight-membered-ring transition state structure. The formation of the eight-membered-ring transition state structure necessitates the acetate oxygen atom to be oriented orthogonally to the xy plane. However, the presence of the phosphine ligand in the upper apex obstructed such a conformation. Instead, the C(sp^3)–H cleavage process occurred through a six-membered-ring structure comprising Pd–C(2)–C(3)–C(10)–H– κ^1 –O, similar to **I_TS3,4**. This process was considerably exergonic by 57.5 kcal/mol with a $\Delta G^\ddagger$ of 11.6 kcal.

To assess the feasibility of the five ACSs, Table 1 summarizes the largest free energy barriers for any individual step ($\Delta G^\ddagger_{i,\text{max}}$, kcal/mol)(ref), as well as the $\Delta G^\ddagger_{\text{max}}$ values for C(sp^2)–H and C(sp^3)–H activations of each species, along with the Gibbs free energies of the product states. The results indicate that among the five species, **IV** is the most promising candidate for the ACS of both C(sp^2)–H and C(sp^3)–H activations of substrate **1**, owing to its lowest $\Delta G^\ddagger_{\text{max}}$ and $\Delta G^\ddagger_{i,\text{max}}$ values for both activation processes. The $\Delta G^\ddagger_{\text{max}}$

and $\Delta G^{\ddagger}_{i,\max}$ values for species **IV** are all 10.6 kcal/mol, which is consistent with the experimentally observed low reaction temperature of 25 °C.

Table 1. Maximum free energy barriers ($\Delta G^{\ddagger}_{\max}$), largest free energy barrier for any individual step ($\Delta G^{\ddagger}_{i,\max}$, kcal/mol), and thermodynamic free energies (ΔG) of C–H activation products for the $C(sp^2)$ –H and $C(sp^3)$ –H activation processes.

	$\Delta G^{\ddagger}_{\max}$ (kcal/mol)		$\Delta G^{\ddagger}_{i,\max}$ (kcal/mol)		ΔG (kcal/mol)	
	$C(sp^2)$ –H	$C(sp^3)$ H	$C(sp^2)$ –H	$C(sp^3)$ H	$C(sp^2)$ –H	$C(sp^3)$ H
I	33.3	51.4	21.4	30.7	23.7	24.7
II	23.8	28.7	23.8	23.8	12.6	−2.6
III	32.0	49.6	21.7	34.4	−15.1	7.5
IV	10.9	10.9	10.9	10.9	−2.9	−18.0
V	36.0	36.0	36.0	36.0	−9.0	−58.1

The presence of the **IV_1** intermediate state provided valuable insight into the reaction mechanism of $C(sp^2)$ –H activation. The Pd–C(2) bond length was found to be within the normal range (2.134 Å) and the C(2)–H and Pd–H distances were 1.090 and 2.573 Å, respectively. This suggests that the C(2)–H bond is not polarized and the metal-to-Hydride interaction is weak, indicating the absence of agostic character in this intermediate state. Notably, the deviation angle (α , Table 2 and Figure 2d) of the hydrogen atom at C(2) from the benzofuran plane was seemingly large (35.8°) compared to those of **I_1**, **II_1**, and **III_1** (9.0°, 17.7°, and 9.8°, respectively). The same was true for the intermediate state **V_1**, with a deviation angle of 45.2°. Since the α value indicates the degree of σ -character in the σ – π continuum of the Pd-substrate adduct [48], this noticeable difference in α values between the Pd(II) and Pd(IV) groups suggests a possible mechanism shift due to changes in the oxidation state of the metal center. The large α value can also be considered as evidence for the existence of a Wheland intermediate and highlights the relationship between the deviation angle and the degree of σ -character in the σ – π continuum of the Pd-substrate adduct.

Table 2. Mayer bond indices (BI^M s), n_0 values (% in parenthesis), and deviation angles (α , °) of ipso hydrogen in the optimized adduct states ^a.

	BI^M			Deviation Angle
	C(2)–C(3)	C(3)–C(4)	C(4)–C(9)	(α , °)
1	1.676 (0)	1.129 (0)	1.261 (0)	
I_1	1.394 (49.6)	1.113 (−6.2)	1.263 (−1.7)	9.0
II_1	1.086 (103.7)	1.054 (−29.1)	1.257 (2.6)	17.7
III_1	1.346 (57.9)	1.105 (−9.5)	1.240 (14.2)	9.8
IV_1	1.083 (104.3)	1.338 (80.1)	1.183 (53.8)	35.8
V_1	1.079 (104.9)	1.337 (79.8)	1.114 (102.3)	45.2
1^{•+}	1.107 (100)	1.389 (100)	1.117 (100)	
ΔBI	0.569	−0.260	0.144	

^a Calculations were performed at B3LYP/def2TZVP/SDD level. BI^M values were calculated by BORDER program [49].

Given the unprecedented computational evidence for the Wheland intermediate, which accompanies S_EAr C–H activation mechanism, we scrutinized the **IV_1** state more thoroughly. Murahashi and coworkers recently reported a method to estimate the degree of σ -character (n_0) in the Pd(II)-indole complex. The n_0 values were evaluated using Mayer bond indices (BI^M) according to the equation, n_0 (complex) [%] = $100 \times [BI^M(\text{N-methylindole}) - BI^M(\text{complex})] / \Delta BI^M$, where $\Delta BI^M = BI^M(\text{N-methylindole}) - BI^M(\text{N-methylindolium})$ [48]. Similarly, n_0 values of the **IV_1** state along with the other intermediates studied herein were calculated with the corresponding BI^M s. In order to select proper bonds for the analyses, we first compared bond lengths of **1** and **1 $\bullet^+$** (see figure in Table 2). The large differences of bond lengths (Δd) between **1** and **1 $\bullet^+$** were found in C(2)–C(3), C(3)–C(4), and C(4)–C(9) bonds and thus we chose these three bonds as the indicators for the quantitative evaluation of n_0 values [48]. The calculated BI^M as well as n_0 values are listed in Table 2.

The degree of σ -character was prominently demonstrated in the intermediate state **V_1**. The calculated n_0 values for the C(2)–C(3) and C(4)–C(9) bonds in **V_1** exceeded 100%, which suggests that **V_1** can be considered a σ -complex. The same holds true for the intermediate state **IV_1**, as the n_0 values for the C(2)–C(3) bond in this state was also above 100%, and the n_0 values for the C(3)–C(4) and C(4)–C(9) bonds were also significantly high (80.1 and 53.8%, respectively). On the contrary, the n_0 values for the three bonds in the Pd(II) catalyst species were lower than those in the Pd(IV) counterpart, indicating that the intermediate states of the former have much less σ -character. The degree of σ -character of these intermediate states was also evaluated in terms of Wiberg bond indices (BI^W) as well as bond lengths (d). The details of these evaluation results are summarized in Supplementary Materials (Table S4). The discrimination in σ -characters between Pd(II) and Pd(IV) groups was again confirmed. The n_0 values with BI^W were -1.0% to 56.2% for the Pd(II) group and 75.9 – 87.8% for the Pd(IV) group. The corresponding values with bond lengths were 37.7% to 39.6% and 73.7% to 88.7% .

The degree of σ -character in the substrate was derived from the charge transfer from the intrinsic π -bond of the substrate to the metal center. In order to provide further evidence for the assertion that the **IV_1** and **V_1** states exhibit pronounced σ -character, we performed a natural bond orbital (NBO) population analysis (Table 3). The corresponding charges (q) of the catalyst and substrate moieties were calculated by summing up the individual charges of the atoms in these moieties. Given that the substrate is intrinsically neutral, the q values of the substrate serve as an indicator of the degree of charge transfer (Δq), which is directly proportional to the σ -character of the intermediates. Our NBO analysis revealed a consistently supported our previous assessments based on Mayer bond indices (BI^M , n_0) or deviation angles (α), with the Pd(IV) group exhibiting higher Δq values (0.782 – 0.815) than the Pd(II) group (0.151 – 0.321). Moreover, visual examination of the three-dimensional mapped surfaces of the electrostatic potential of the intermediates further highlights the discernible differences between the Pd(II) and Pd(IV) groups (Figure 7), with the contrast between the catalyst and substrate moieties being particularly pronounced in the Pd(IV) species.

Table 3. Charge distribution of catalyst and substrate moieties of n_1 intermediate states ($n = \text{I–V}$) obtained by NBO population analysis.

	Q^a		Δq^b
	Catalyst	Substrate	
I_1	−0.151	0.151	0.151
II_1	−0.321	0.321	0.321
III_1	−0.172	0.172	0.172
IV_1	0.218	0.782	0.782
V_1	0.191	0.809	0.809

^a Summed charge of the moiety. ^b The amount of charge transferred from substrate to Pd metal.

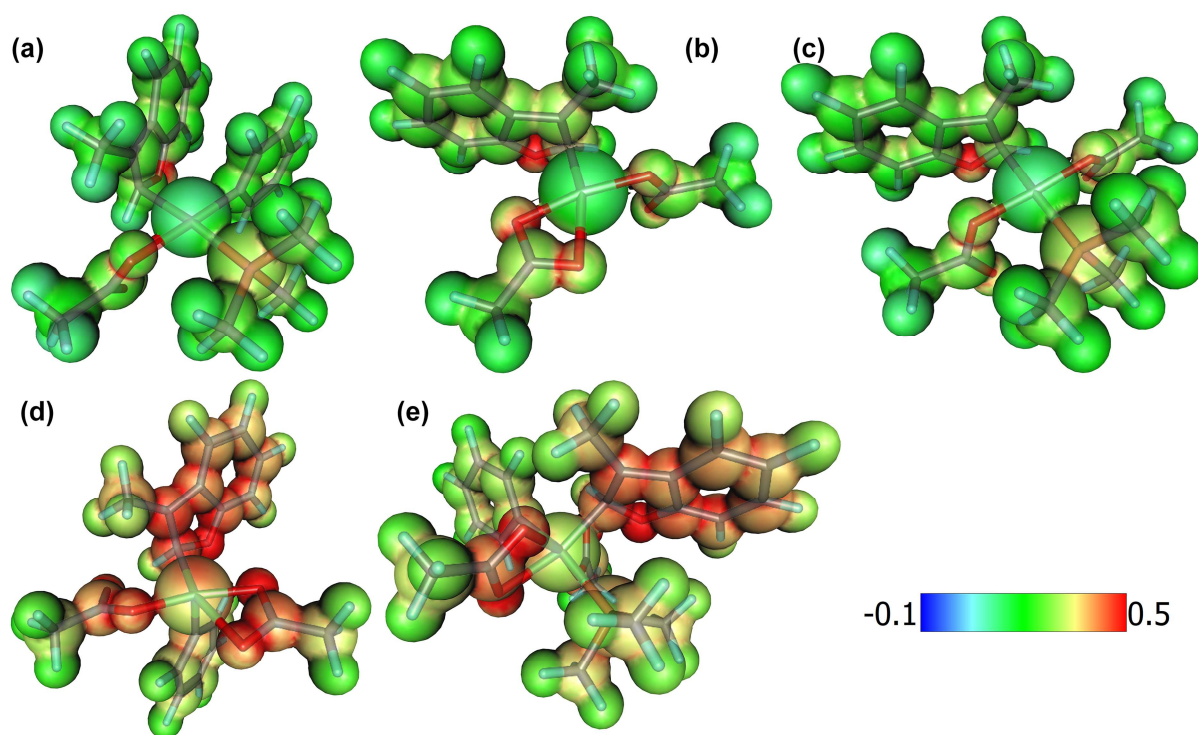


Figure 7. Mapped sphere of electrostatic potential in the -0.1 – 0.5 range: (a) **I_1**, (b) **II_1**, (c) **III_1**, (d) **IV_1**, and (e) **V_1**.

We established a correlation between the parameter α and the averaged n_0 values over the C(2)–C(3), C(3)–C(4), and C(4)–C(9) bonds as well as between α and Δq . These relations are co-plotted and graphically displayed in Figure 8. The graphs clearly show that the Pd(II) and Pd(IV) groups occupy distinct regions on the σ – π continuum thereby being characterized as π -complexes and σ -complexes, respectively. It is important to note that since the intermediate state **IV_1a** generated by the most probable ACS **IV** belongs to the σ -complex, confirming the Wheland nature of these states, the mechanism of C(sp^2)–H activation of 3-methylbenzofuran by catalyst **IV** can be regarded as S_EAr .

In recent years, activation strain analysis (ASA) has become increasingly popular in the field of organic synthesis, as it offers a valuable tool for predicting and rationalizing the outcomes of chemical reactions. ASA is a theoretical method used in computational chemistry to understand the factors controlling the reactivity and mechanism of organic reactions by analyzing the energies to distort isolated reactants to the transition state geometry (the distortion energy) and the energy of interaction between these distorted reactants (the interaction energy). Recently, this method has been successfully applied to analyze the reactivity of oxidative addition [50,51] and C–H bond activation [52]. To cast light on the reactivities of five ACSs studied in our work, we performed ASA for both C(sp^2)–H and C(sp^3)–H activation processes by five ACSs (Scheme 3). The analysis results are listed in Table 4.

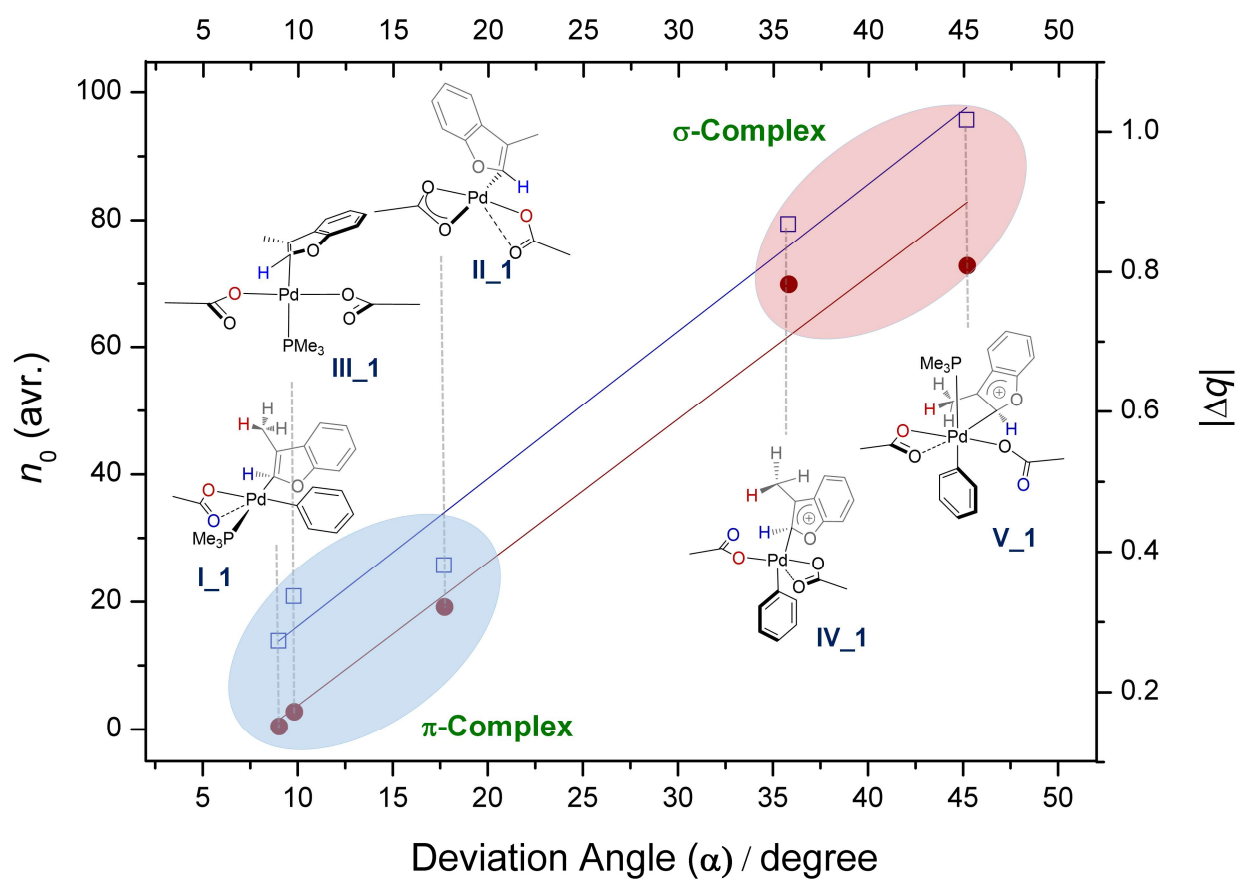
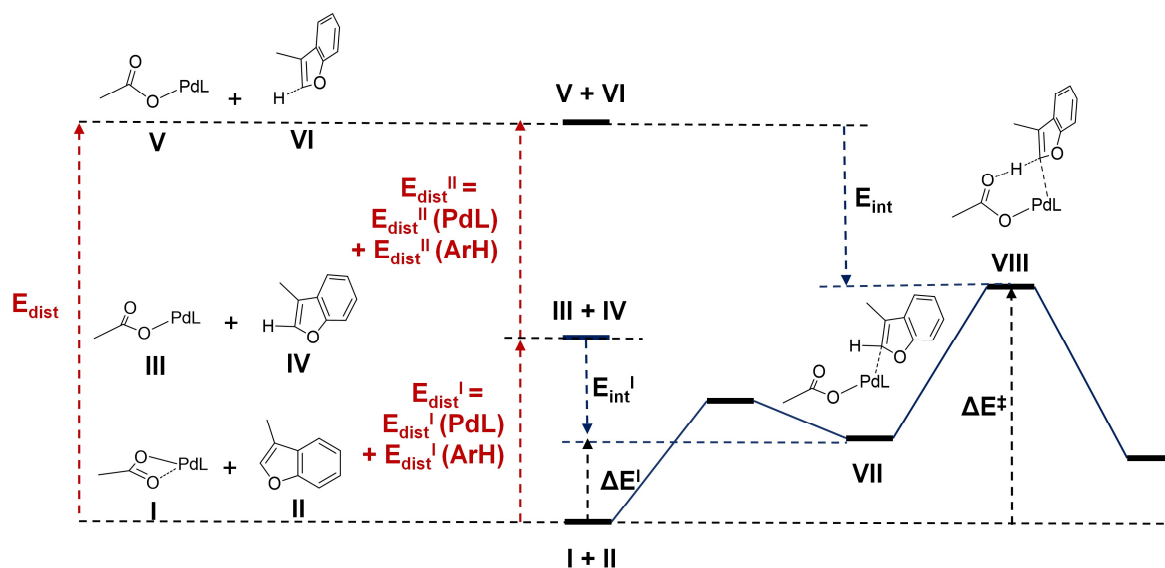


Figure 8. Correlation diagram of α vs. n_0 (avr.) (blue open square) and α vs. $|\Delta q|$ (dark red closed circle).



Scheme 3. Activation strain analysis.

Table 4. Activation strain analysis results. Catalyst and substrate distortion energies, metal–arene interaction energies of C(*sp*²)–H and C(*sp*³)–H cleavage processes by five different ACSs ^a.

Path	$E_{\text{dist}}^{\text{I}}$ (PdL) ^b	$E_{\text{dist}}^{\text{I}}$ (ArH) ^c	ΔE^{I}	$E_{\text{dist}}^{\text{II}}$ (PdL) ^d	$E_{\text{dist}}^{\text{II}}$ (ArH) ^e	E_{int}	$\Delta E^{\ddagger}$	$E_{\text{dist}}^{\text{I f}}$	$E_{\text{dist}}^{\text{II g}}$
I (<i>sp</i> ²)	8.5	1.6	6.9	4.3	38.5	−30.2	22.7	10.1	42.8
I (<i>sp</i> ³)	8.5	1.6	6.9	8.5	57.3	−35.9	40.1	10.1	65.9
II (<i>sp</i> ²)	14.2	5.9	−2.4	2.6	27.9	−42.5	8.1	20.1	30.5
II (<i>sp</i> ³)	14.2	5.9	−2.4	8.3	49.7	−63.1	15.0	20.1	58.1
III (<i>sp</i> ²)	5.2	1.4	3.8	4.2	39.4	−31.5	18.6	6.6	43.6
III (<i>sp</i> ³)	5.2	1.4	3.8	7.9	34.8	−17.8	31.5	6.6	42.7
IV (<i>sp</i> ²)	13.2	16.3	−17.3	6.1	25.0	−71.6	−11.1	29.4	31.1
IV (<i>sp</i> ³)	13.2	16.3	−17.3	10.3	33.3	−85.0	−12.0	29.4	43.6
V (<i>sp</i> ²)	30.3	21.8	6.4	3.3	21.1	−69.9	6.5	52.1	24.4
V (<i>sp</i> ³)	30.3	21.8	6.4	8.3	37.7	−79.8	18.2	52.1	45.9

^a All listed energies are electronic energies. ^b Distortion energy of the catalyst moiety of the pre-C–H cleavage intermediate state. ^c Distortion energy of the 3-methylbenzofuran moiety of the pre-C–H cleavage intermediate state. ^d Distortion energy of the catalyst moiety of the C–H cleavage transition state— $E_{\text{dist}}^{\text{I}}$ (PdL). ^e Distortion energy of the 3-methylbenzofuran moiety of the C–H cleavage transition state— $E_{\text{dist}}^{\text{I}}$ (ArH). ^f $E_{\text{dist}}^{\text{I}}$ (PdL) + $E_{\text{dist}}^{\text{I}}$ (ArH). ^g $E_{\text{dist}}^{\text{II}}$ (PdL) + $E_{\text{dist}}^{\text{II}}$ (ArH).

In the present analysis, the distortion energy necessary to achieve a transition state geometry is partitioned into two components: one corresponding to the conversion from the initial state (**X**₀, **X** = **I**–**V**) where the catalyst and substrate are separated, to the intermediate state (**X**₁) geometry ($E_{\text{dist}}^{\text{I}}$); and the other associated with the transition from the intermediate geometry to the transition state (**X**_{TS1,2}) geometry ($E_{\text{dist}}^{\text{II}}$). By this way, we were able to discern dissimilar properties of the intermediates that manifest depending on the different ACS. Specifically, in the case of the Pd(II) catalyst (**I**–**III**), $E_{\text{dist}}^{\text{II}}$ is considerably greater than that in step I, whereas for the Pd(IV) catalyst, $E_{\text{dist}}^{\text{I}}$ and $E_{\text{dist}}^{\text{II}}$ are similar to each other (**IV**), or $E_{\text{dist}}^{\text{I}}$ is even greater than $E_{\text{dist}}^{\text{II}}$ (**V**). This can be attributed to the distinctive nature of the intermediate species formed in the case of Pd(IV), wherein the C–H bond undergoes a significant loss of its original *sp*² character and gains an *sp*³ character that closely resembles the structure of the transition state. As a result, $E_{\text{dist}}^{\text{II}}$ is primarily governed by the lengthening of the C–H bond, rather than the *sp*² to *sp*³ transformation of the C–H bond. As such, our analysis provided further corroboration of the formation of a Wheland intermediate in the case of Pd(IV) catalyst, ascertained through ASA.

Besides this information, ASA enabled us to determine the origin of the relative activation barriers of C(*sp*²)–H and C(*sp*³)–H activations through a comparison of the total distortion energy and interaction energy (Table S6). We observed that E_{dist} was the dominant factor for **I**, **II**, and **V**, while interaction energy was the dominant factor for catalyst **III**. Notably, for catalyst **IV**, C(*sp*²)–H bond activation was slightly more disadvantageous than C(*sp*³)–H counterpart mainly due to the relatively small difference in distortion energy between the two activations. This trend was also observed in **III**, as the eight-membered-ring transition state structure for C(*sp*³)–H activation did not require significant distortion of the substrate. However, in the case of **II**, the significant difference in distortion energy between C(*sp*²)–H and C(*sp*³)–H activations is attributed to **II**_{TS1,3}, which constitutes an eight-membered-ring transition structure with strong Pd–C(2) sigma bonding, causing the C(2)–H atoms to be severely out of the 3-methylbenzofuran ring plane. Our analysis thus provided a more comprehensive and three-dimensional understanding of the ACS through ASA. Besides the aforementioned information, ASA allowed us to determine the origin of the difference between $E^{\ddagger}$ values of C(*sp*²)–H and C(*sp*³)–H activations by comparing the E_{dist} and E_{int} (Table S6). Our findings revealed that E_{dist} was the dominant factor for catalysts **I**, **II**, and **V**, while E_{int} was the dominant factor for catalyst **III**. Notably, for catalyst **IV**, C(*sp*³)–H bond activation was slightly more advantageous than its C(*sp*²)–H counterpart mainly due to the relatively small difference in E_{dist} between

the two activations. This trend was also observed in catalyst **III**, as the eight-membered-ring transition state structure for $C(sp^3)-H$ activation did not require significant distortion of the substrate. However, in the case of catalyst **II**, the significant difference in E_{dist} between $C(sp^2)-H$ and $C(sp^3)-H$ activations is attributed to **II**_TS_{1,3}, which constitutes an eight-membered-ring transition structure with strong Pd–C(2) σ bonding, causing the C(2)–H atoms to be severely bent out of the 3-methylbenzofuran ring plane. Thus, our ASA provided a more comprehensive understanding on the nature of catalytic C–H activation reactions undergo by five ACSs studied in this work.

3. Computational Methods

The calculations were performed using the Gaussian 09 [53] and Gaussian 16 [54] program packages. All results were obtained using a spin-restricted formalism at the DFT using the B3LYP hybrid functional [55–57]. All geometries of stationary states were fully optimized without any symmetry restriction. The palladium, silver, and iodine atoms were described by LANL2DZ basis set with the relativistic effective core potential (ECP) of Hay and Wadt for the inner electrons and a double- ζ basis set for the outer electrons. The standard 6–31G(d) basis set was used for the remaining atoms. Single point frequency calculations were then performed to characterize the stationary points as minima or transition states. Transition states (TS) were identified by only one imaginary frequency that corresponds to the vibrational mode of the given bond breaking/bond making. The Karlsruhe basis sets in triple- ζ level were used for all atoms [58,59]. The relativistic ECPs for the inner 28 electrons of palladium [60], silver [61], and iodine [62] atoms were represented by the Stuttgart RSC 1997 (SDD). Solvation corrections were added using a self-consistent reaction field (SCRF) approach [63–65] by a conductor-like polarizable continuum model (CPCM) [66,67] in water ($\epsilon_{\text{water}} = 78.3553$). Intrinsic reaction coordinate (IRC) calculations were performed to ensure that the TS actually connects the proposed reactants and products.

4. Conclusions

We conducted a DFT study to elucidate the reaction mechanisms of carboxylate-assisted $C(sp^2)-H$ and $C(sp^3)-H$ activations of 3-methylbenzofurans to 3-methyl-2-phenylbenzofurans or 3-benzylbenzofuran with five hypothetical catalyst species: $[\text{Pd}(\text{OAc})(\text{PMe}_3)(\text{Ph})]$ (**I**), $[\text{Pd}(\text{OAc})_2]$ (**II**), $[\text{Pd}(\text{OAc})_2(\text{PMe}_3)]$ (**III**), $[\text{Pd}(\text{OAc})_2(\text{Ph})]^+$ (**IV**), and $[\text{Pd}(\text{OAc})_2(\text{PMe}_3)(\text{Ph})]^+$ (**V**) as potential ACS candidates. The information obtained in this work is as follows: (1) $[\text{Pd}(\text{OAc})_2(\text{Ph})]^+$ (**IV**) in the Pd(IV) oxidation state among five candidates was found to be the most favorable. The calculated reaction pathways catalyzed by **IV** exhibited smooth cascade-type energy profiles with 10.9 kcal/mol of $\Delta G^\ddagger_{\text{max}}$ for both $C(sp^2)-H$ and $C(sp^3)-H$ activations. This result indicated that the inclusion of a phosphine ligand may not be crucial in the catalytic reaction conditions for the C–H activation of heteroarenes. (2) For the $C(sp^3)-H$ activation conducted by catalysts **II**, **III**, and **IV**, the eight-membered-ring transition state structural motif was found to be more favorable than the conventional six-membered-ring counterpart. (3) Catalyst species in the Pd(IV) oxidation states forms a Wheland intermediate. This intermediate has a strong σ -character supported by the facts that (i) the significant partial charge transfer from the substrate to the metal center was determined by an NBO population analysis, (ii) the high degree of n_0 value was judged by bond length, Mayer and Wiberg bond indices of the furan ring, and (iii) a significant deviation angle (α) is pronounced between the C(2)–H bond and the benzofuran plane. These findings are of an unprecedented computational study that reveals the evidence of a Wheland intermediate in the $C(sp^2)-H$ activation. (4) The existence of the Wheland intermediate suggests that the reaction mechanism of $C(sp^2)-H$ activation is likely S_EAr , indicating that a given reaction can potentially proceed through distinct mechanisms depending on the employed active catalytic species. As such, consideration of diverse ACS is crucial in understanding more precise and comprehensive insights into the reaction mechanism in the computational study.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/catal13040724/s1>. Full reference of Gaussian 09 and 16 program; Table S1: Energies of local minima stationary points; Table S2: Energies and imaginary frequencies of transition states; Table S3: Atomic coordinates for stationary points; Figure S1: Free energy reaction profile for the generation of IV and V from II; Table S4: Optimized structural parameters, Wiberg bond indices, n_0 values, and deviation angle of ipso hydrogen of intermediate states; Table S5: Mapped surfaces of electrostatic potential of intermediate states; Table S6: Distortion–interaction analysis.

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