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Mechanistic Insights into the Pd-Catalyzed Carbonylation of Alkynol for α-Methylene-β-Lactone Formation

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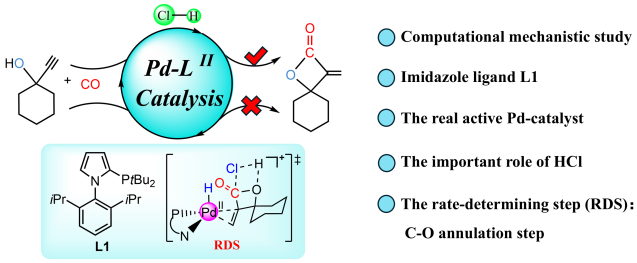
Abstract: Density functional theory (DFT) calculations were performed to elucidate the reaction mechanism of the Pd-catalyzed carbonylation of propargylic alcohol **(1)**, leading to the efficient synthesis of cyclohexyl α-methylene-β-lactone **(2)**. Our study revealed that the reaction proceeds through a four-step pathway: alkyne migration and insertion, CO insertion, HCl-assisted hydrogen transfer, and final C–O annulation. Notably, the final C–O annulation step was identified as the rate-determining step (RDS) of the overall catalysis, with a free energy barrier of 25.7 kcal/mol (i.e., **IM4→TS4**). Additionally, we uncovered the critical role of the HCl during the reaction pathway, a demonstrating that it acts as a co-catalyst, proton shuttle, and hydrogen bond donor/acceptor. NBO, EDA-NOCV, and HIGM analyses further revealed that the remarkable stability of the transition state **TS3** in the presence of HCl primarily arises from strong electrostatic attraction and orbital interaction energies between the two interacting fragments. These mechanistic insights provide valuable insight and guidance for the rational design of new Pd-catalyzed transformations.



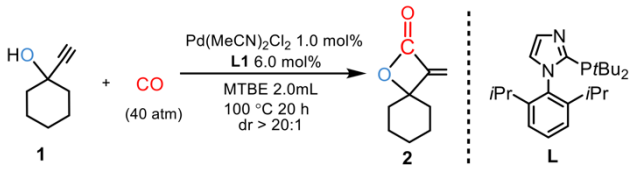
Key words: Reaction mechanism, α-Methylene-β-Lactones, Pd-catalyst, NBO analysis, EDA-NOCV analysis.

1. Introduction

α-Alkylidene-β-lactones are vital functional groups found in various biomolecules and pharmaceuticals, making them highly significant in medicinal chemistry [1,2].Their widespread occurrence in natural compounds and biologically active molecules has established them as key synthetic targets in organic synthesis [1-6], while their applications in materials science have also garnered considerable interest. Notably, α-methylene-β-lactones are particularly valuable due to their potential in ring-opening polymerization, enabling the synthesis of copolymers with well-defined architectures, controlled molecular weights, and narrow polydispersity [7, 8] . In organic synthesis, the highly functionalized and compact structure of α-alkylidene-β-lactones provides diverse synthetic opportunities, making them versatile intermediates for further chemical transformations [9-15]. Additionally, their four-membered ring system is inherently strained, facilitating ring-opening reactions with various nucleophiles via acyl C-O or alkyl C-O bond cleavage [9, 16]. Given their synthetic importance, extensive efforts have been devoted to developing efficient methodologies for their preparation [17-22]. Reported strategies include [2+2]-cycloaddition of ketenes [23-26], lactonization of β-

hydroxycarboxylic acids and their derivatives [11, 17, 20, 21], selenoxide elimination from α-methyl-substituted lactones [27], and deoxygenation of β-peroxylactones [22, 28].

In 2020, Beller and co-workers reported the first general and highly selective Pd-catalyzed carbonylation of propargylic alcohols, leading to the efficient synthesis of α-methylene-β-lactones (i.e., **2**) [29]. This groundbreaking strategy highlights the pivotal role of Pd(II)-catalyst in achieving selective catalytic transformations. As shown in Scheme 1, the reaction proceeds under the catalytic influence of a phosphine palladium complex based on a 1-(2,6-diisopropylphenyl)-1H-imidazole ligand (**L-Pd**), where propargylic alcohol (**1**) undergoes carbonylation with CO, delivering the target product with high yield and excellent regioselectivity.



Entry	Additive	Yield 2(%)
1	none	0
2	HCl (2 mol%)	98 ✔

Scheme 1. Pd-catalyzed carbonylation of propargylic alcohols reported by Beller [29].

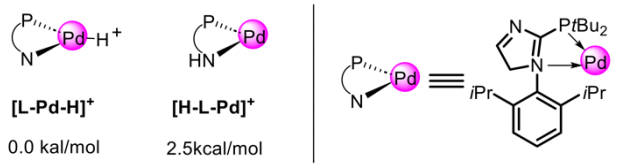
Although the authors proposed a plausible reaction pathway, several key aspects remain unresolved, including what the real active Pd-catalyst is, the role of HCl during the reaction pathway, and the identification of the rate-determining step (RDS) in the overall catalytic cycle. To bridge these gaps, we conducted a comprehensive density functional theory (DFT) study to elucidate the reaction mechanism of this transformation (Scheme 1). The mechanistic insight will not only enhance our understanding of the reaction but also provide a foundation for optimizing existing catalytic systems and guiding the development of new Pd-catalyzed strategies for α-alkylidene-β-lactone synthesis.

2. Theoretical method

Geometry optimizations were carried out with the Gaussian 16 program [30] and the structures were illustrated by CYLview [31]. Specifically, geometry optimizations without symmetry restriction were firstly optimized at the BP86 [32, 33]/def2-SVP [34, 35] level augmented with Grimme's D3 [36] dispersion corrections. Previous studies also calibrated the good performance of the BP86 functional for the Pd catalyzed reactions [37-39]. The solvation effects of the experimentally used solvent (i.e., toluene) were taken into consideration by using the integral equation formalism variant of polarizable continuum model IEFPCM [40]. Vibrational frequency calculations were performed at the same level of theory to characterize the stationary points as either local minima (no imaginary frequencies) or transition structures (one imaginary frequency) on the potential energy surface, and to obtain the thermochemical corrections for the Gibbs free energies. Intrinsic reaction coordinate (IRC)[41] calculations were conducted to verify the critical reaction steps involved in our proposed mechanisms. The energetic results were further improved by the single-point calculations at the BP86-D3/def2-TZVPP [42] level with the solvation effects included. For comparison, the performance of several popular DFT functionals (e.g., B3LYP [43-45] , M06[46-48], B97D [49] and M06-L [50]) was studied on intermediate **IM4** (see Table S1), implying that the BP86 functional used in this study is reliable. Unless otherwise statement, the BP86-D3/def2-TZVPP (IEFPCM, solvent=toluene)//BP86-D3/def2-SVP (IEFPCM, solvent=toluene) Gibbs free energies (in kcal/mol) are used in the following discussion, while the electronic energies are also given in the related figures for reference. Spin natural orbital (SNO) analysis is given by Multiwfn 3.8 software [51]. NBO [52] calculations have been performed using NBO 3.1 program [53] implemented in the Gaussian 16 package at the same level of theory , The independent gradient model based on Hirshfeld partition (IGMH) [54] was employed to investigate the weak interactions of the transition state **TS3**,**TS3'** and **TS3''**, Using the AMS2024 program at the BP86/def2-SVP level,the nature of the bond in the transition state **TS3**,**TS3'** and **TS3''** was analyzed by combining the energy decomposition analysis (EDA) [55] with the natural orbital for chemical valence (NOCV) [56, 57].

3. Results and discussion

In this study, we first optimized two possible conformations of the cationic active palladium species. As shown in Scheme 2, **[L-Pd-H]**$^+$ is 2.5 kcal/mol more stable than its isomer **[H-L-Pd]**$^+$, implying that **[L-Pd-H]**$^+$ is the more favorable species and should be selected as the reference state for subsequent mechanistic investigations. The energetics results for the formation of the active **[L-Pd-H]**$^+$ species starting from the pre-catalyst $Pd(MeCN)_2Cl_2$ are provided in Figure S2. Notably, similar cationic active palladium species has been widely used in in previous studies [58, 59].



Scheme 2. Gibbs free energy difference for the **[L1-Pd-H]**$^+$ and **[H-L1-Pd]**$^+$ isomer.

Figure 1 presents the calculated free energy profiles for the formation of the α-methylene-β-lactone product (**2a**). Due to the coordination unsaturation of the cationic palladium hydride species [L-Pd-H]$^+$, which renders it structurally unstable, this species readily coordinates with carbon monoxide (CO) to form a more stable intermediate [L-Pd(CO)H]$^+$. Subsequently, the CO ligand in [L-Pd(CO)H]$^+$ is replaced via a ligand exchange process with the alkyne substrate (1), leading to the formation of the weakly coordinated palladium–alkyne complex **IM1**. In **IM1**, the H-atom in **[L-Pd-H]**$^+$ readily migrates to the terminal carbon of the alkyne (**1**) with a very low free energy barrier of 1.7 kcal/mol (i.e., **IM1→TS1**), yielding the slightly more stable intermediate **IM2**. In addition, we examined an alternative migratory insertion pathway involving a 1,2-insertion mode. However, the free energy barrier for the 1,2-insertion is 3.8 kcal/mol higher than that of the 2,1-insertion pathway (see Figure S3), implying that the 2,1-insertion pathway is kinetically more favorable, which agree well with experimentally observed selectivity.