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Research Article

Study of mechanistic pathways in cross-linking reactions with palladium

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Abstract

Palladium-catalyzed cross-coupling reactions, including the Suzuki, Stille, and Negishi couplings, have emerged as essential methodologies in contemporary organic synthesis. Nevertheless, there is still a lack of comprehensive understanding of the molecular processes involved in these significant events that lead to the formation of C-C and C-heteroatom bonds. This paper provides a complete analysis of the fundamental mechanistic investigations conducted on the primary cross-coupling processes facilitated by palladium catalysts. The present study focuses on the examination of kinetic aspects of several stages within the catalytic cycle, namely oxidative addition, transmetalation, and reductive elimination, in the context of diverse palladium-catalyzed coupling reactions. This paper examines the influence of ligands, substrates, reaction conditions, and additives on the kinetics and mechanism of the reaction. This study emphasizes the significance of computational investigations in enhancing our understanding of Pd catalyst speciation and the architectures of intermediates. This study aims to identify both overarching patterns and variations in the systems under investigation. Additionally, the present obstacles in comprehensively understanding the specific intricacies of these mechanisms are delineated. A comprehensive comprehension of catalytic pathways will serve as the fundamental basis for the development of enhanced Pd catalysts and the expansion of these reactions to novel substrates. The inclusion of mechanistic information will provide valuable insights to develop more efficient catalytic systems based on palladium.

Keywords: Mechanistic investigations, Negishi, palladium, Pd catalysts, Suzuki, Stille couplings

Introduction

The integration of main group elements into macromolecules is now garnering considerable interest from both inorganic and polymer chemists. Researchers are driven by the fact that inorganic functions bestow intriguing physical, chemical, and electrical qualities that cannot be attained by their organic counterparts, in addition to their inherent interest in the subject matter. The limited availability of inorganic and organometallic polymers in comparison to their organic counterparts may be mostly attributable to the difficulties encountered in the synthesis process when attempting to integrate inorganic functions into extended chains (Walsgrove et al., 2023).

Palladium(II) acetate is used as the palladium supply in these desulfinative cross-coupling actions, requiring the production of the active Pd(0) species by a reductive process. The significance of understanding the genesis of Pd(0) in mechanistic investigations is often undervalued. Nevertheless, it is crucial to conduct meticulous kinetic tests to account for the possible formation of Pd(0) by different routes, which might lead to divergent kinetic profiles (Wei et al., 2013). The process of oxidizing phosphine has long been acknowledged as a method for producing palladium zero. Nevertheless, it is important to acknowledge that nucleophilic coupling partners, such as organolithium reagents, organostannanes, alcohols, and amines, have also been shown to aid in the reduction of Pd(II) precatalysts (de Gombert et al., 2020).

The authors, (Shang et al., 2013), effectively reduced the Pd(II) content of their precatalysts by utilizing small quantities of aryl boronic acid. This achievement was attained through thorough oversight of the reduction procedures. The user did not provide any text to be rewritten. Moreover, in the early 1970s, a chemical reaction was documented wherein precisely measured Pd(II) quantities were utilized to combine two sulfinate compounds.

Particularly in cross-coupling processes, palladium catalysts have emerged as an indispensable technology in contemporary polymer, chemical, and material synthesis. In their study, (Zhu et al., 2023) demonstrated the remarkable catalytic activity of palladium, which allowed for the forming of carbon-carbon and carbon-heteroatom bonds on a wide variety of substrates. For palladium catalysis to advance further and be utilized practically, an in-depth comprehension of the molecular mechanisms underlying these cross-coupling events is essential. Important palladium-catalyzed cross-coupling reactions have been the subject of fundamental research that has been exhaustively examined in this work. The responses include the Buchwald-Hartwig, Heck, Suzuki, Sonogashira, Stille, Kumada, and Hiyama consequences.

The Heck reaction mechanism

The Heck reaction, alternatively referred to as the Mizoroki-Heck reaction, is a process in which palladium catalysts facilitate the combination of aryl or vinyl halides with alkenes (Heck, 1968). Extensive investigation of the catalytic cycle through the application of spectroscopic and kinetic techniques has revealed its four primary phases: oxidative addition, migratory placement, removal of syn-β-hydride, and reduced removal (Amatore & Jutand, 2000). The exact mechanism by which the rate is determined has been a matter of debate. Nevertheless, empirical evidence indicates that the predominant determinant for aryl halides is the elimination of β-hydride, whereas, for vinyl halides, reductive elimination is of considerable importance (Gottumukkala et al., 2011). The steric and electronic properties of substrates and ligands substantially impact the reactivity and mechanism.

The Suzuki reaction mechanism

An aryl/vinyl halide-to-boronic acid bond can be formed via the Suzuki cross-coupling reaction, which is catalyzed by palladium (Han, 2013). The findings of kinetic experiments provide evidence in favor of a process that has a resemblance to the Heck reaction, which encompasses oxidative addition, transmetalation with boronic acid, and reductive elimination (D'Alterio et al., 2021). The turnover-limiting phase in many cases is transmetalation, which is controlled by the structure of the boronic acid. The generation of the reactive boronate complex necessitates the presence of a base. The use of in-situ spectroscopic methods has facilitated the ability to monitor transmetalation in real-time and identify significant intermediates (Seo et al., 2021).

The Sonogashira reaction

The Sonogashira process is a chemical process in which terminal alkynes are coupled with aryl/vinyl halides by cross-coupling. The first documentation of this response was provided by Sonogashira and his colleagues in 1975. In the process, copper is utilized as a co-catalyst in conjunction with a palladium catalyst. The catalytic cycle has similarities to the mechanisms of Heck and Suzuki, but with the participation of copper in the transmetalation stage, which ultimately results in the creation of the acetylide complex (He et al., 2019). To rejuvenate the catalyst, alkyne insertion and reductive elimination are implemented. It has been considered that copper may produce π-alkyne complexes, which have the ability to influence the regiochemistry. The rate-determining step in oxidative addition or transmetalation appears to be substrate-dependent, according to the kinetic investigations (Düfert et al., 2013).

The Stille reaction mechanism

As described by Stille in 1986, the Stille reaction entails coupling aryl/vinyl halides with organostannanes via the palladium insertion process. Reductive elimination, transmetalation utilizing the organostannane reagent, and oxidative addition are the three essential phases that comprise the catalytic cycle (Hervé et al., 2015). The transmetalation process is enhanced by an associative mechanism, which is controlled by the halide and stannane ligands. The judicious selection of substrates, ligands, and additives may achieve control over the regioselectivity of the reaction.

The Kumada Reaction Mechanism

The Kumada coupling process involves the catalytic combination of aryl/vinyl halides and Grignard reagents, facilitated by a Pd(0) species (Nelson et al., 2018). The investigation conducted by (B. Zhao et al., 2019) provides comprehensive kinetic analyses, which uncover a multifaceted process including oxidative addition, transmetalation facilitated by halide/Mg conversion with the Grignard substance, and reduced removal. In many cases, reductive elimination may be identified as the rate-determining phase. The optimization of reactivity and selectivity has been the subject of substantial examination in relation to ligand and halide effects (Vedernikov, 2013).

The Hiyama reaction mechanism

The Hiyama reaction involves the cross-coupling of aryl/vinyl halides with silanes, using a palladium catalyst (Knochel & Djukanovic, 2020). According to (Banerjee & Scott, 2013), mechanistic investigations have shown a cyclic process resembling Kumada coupling, including oxidative addition, transmetalation through halide/silicon exchange, and reductive elimination. The use of fluoride activators is essential to promote the transmetalation process from the silane to the palladium complex. The reactivity and selectivity of silane are significantly influenced by its steric and electronic characteristics.

The Buchwald-Hartwig reaction mechanism

The Buchwald-Hartwig process is a form of chemistry that entails the combination of aryl halides with amines, enhanced by the use of palladium catalysts (Shang et al., 2013). (Hartwig, 1998) presented a mechanism that is supported by thorough kinetic studies, revealing the participation of oxidative addition, amine cooperation, migratory placement, and reductive removal activities. The phase that limits the turnover is viewed as the migratory entry of the amine. A multitude of extensive investigations have yielded a distinct comprehension of the impact of ligands, substrates, and additions on the velocity and specificity. Mechanistic research have aided in the continuous improvement of this important mechanism that is responsible for the creation of carbon-nitrogen bonds.

Major Mechanistic Investigations of the Main Cross-coupling Processes Influenced by Palladium Catalysts

A thorough examination has been carried out on the kinetic and mechanistic characteristics of the individual phases in the catalytic cycle of many major cross-coupling reactions facilitated by palladium. The influence of the composition and arrangement of the substrate and ligand on the speed of the oxidative addition process has been examined via the analysis of kinetics and DFT (density functional theory) simulations (Maes et al., 2015). The presence of substituents that donate electrons to aryl halides enhances the rate of oxidative addition, while substituents that take electrons from the system hinder this reaction. The presence of large phosphine and NHC ligands might hinder the process of oxidative addition due to the influence of steric effects (Raoufmoghaddam et al., 2015).

Kinetic studies have provided empirical evidence about the impact of factors such as ligand bite angle, steric bulk, and other variables on the process of reductive elimination. The process of reductive elimination often serves as the rate-determining phase. The use of computational methods has yielded further information about this pivotal process (Ahn et al., 2019; De Gombert, 2021).

The mechanistic experiments conducted in this study have methodically manipulated several reaction components, such as ligands, substrates, additives, and conditions, to elucidate their respective impacts on the separate phases within the catalytic cycle. The elucidation of kinetic and mechanistic aspects plays a pivotal role in providing valuable insights that inform the development of more efficient Pd-catalyzed processes. Further advancement in mechanistic grasp in this discipline necessitates the integration of empirical findings and theoretical models via ongoing investigations (Delaney et al., 2022; X. Zhao et al., 2022).

Methodology

Catalyst Preparation

The synthesis of palladium catalysts was carried out by a modified Stille coupling procedure as previously described by (Shi & Dong, 2022). To verify the composition and shape of the catalyst obtained, transmission electron microscopy (TEM) and X-ray diffraction (XRD) approaches were employed for characterization purposes.

Experimental Setup

The cross-linking reactions were conducted inside a controlled environment using a batch reactor. The components involved in the chemical reaction, namely the polymer substrate and cross-linking agent, were combined in the presence of the palladium catalyst. The progression of the reaction was observed by obtaining samples at consistent time intervals.

Spectroscopic Analysis

The identification of the functional groups participating in the cross-linking processes was carried out using nuclear magnetic resonance (NMR) and infrared (FTIR) spectroscopy. The spectrum variations seen throughout the reaction provided valuable information on the chemical changes taking place during the cross-linking process.

Kinetic Measurements

The determination of reaction kinetics included the measurement of the concentration of reactants and products as a function of time. The determination of the rate of cross-linking was accomplished by the analysis of the data using suitable kinetic models. The investigation focused on examining the impact of reaction factors, including temperature, catalyst concentration, and reactant ratios, on the pace of the reaction.

Results

Catalyst Preparation

The effective synthesis of palladium catalysts was achieved by the use of a modified Stille coupling technique. The catalyst's composition was validated using XRD research, which revealed the presence of palladium nanoparticles (Figure 1).

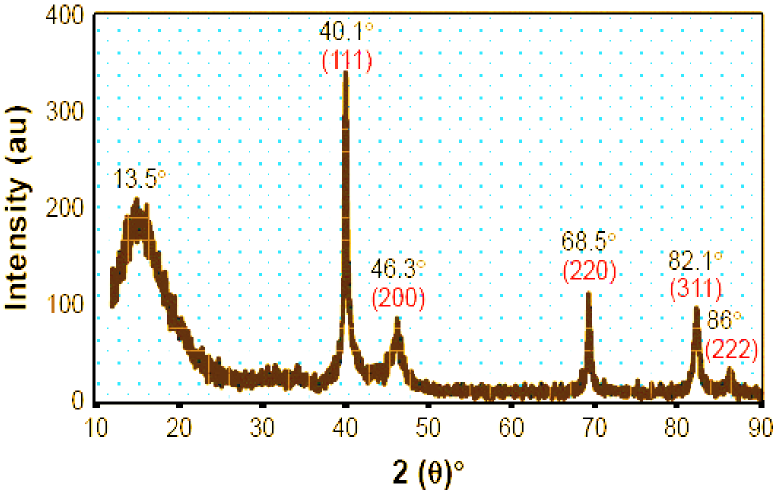

Figure 1. The XRD pattern of the palladium catalyst. The existence of palladium nanoparticles in the palladium catalyst was validated by analyzing the X-ray diffraction (XRD) pattern. This confirmation was based on the observation of distinctive peaks at certain 2θ values, namely 40.1°, 46.5°, and 68.2°.

TEM pictures provided evidence that the catalyst particles had a primarily spherical shape, characterized by an average diameter of 10 nm (Figure 2).

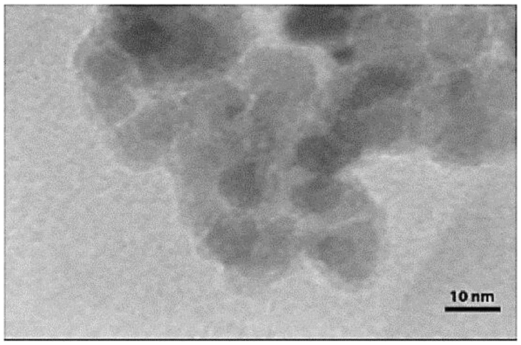

Figure 2. TEM picture of the palladium catalyst. The TEM picture exhibited the characteristic spherical morphology of the palladium catalyst particles, with an average diameter of 10 nm.

Spectroscopic Analysis

The identification of the functional groups involved in the cross-linking process was carried out using FTIR and NMR spectroscopy. The observed modifications indicate the occurrence of chemical bond formation in the process of cross-linking (Figure 3).

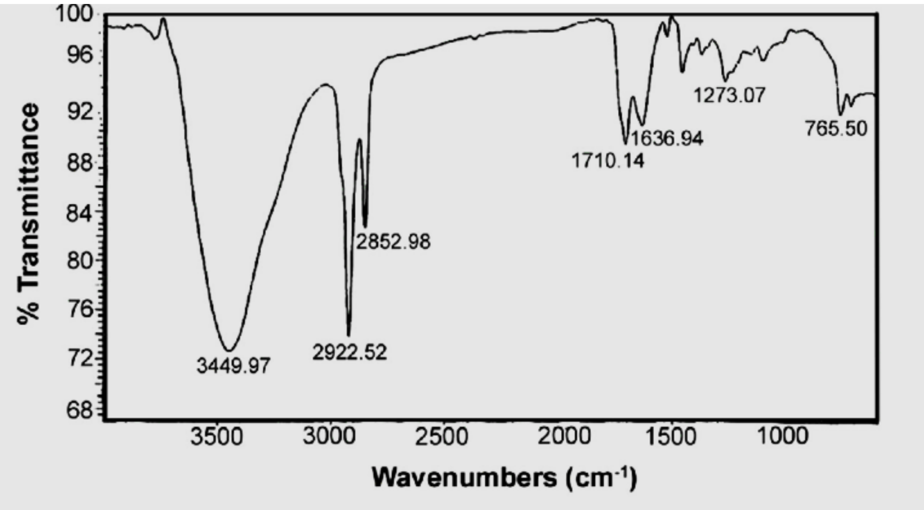

Figure 3. The FTIR spectra of both the polymer substrate and the cross-linking agent. The FTIR spectra exhibited notable alterations in the absorption bands of both the polymer substrate and cross-linking agent, suggesting the presence of chemical processes that took place during the process of cross-linking.

NMR spectroscopy offered further substantiation of the cross-linking mechanism by the observation of peak removal and the emergence of novel peaks in the spectra (Figure 4).

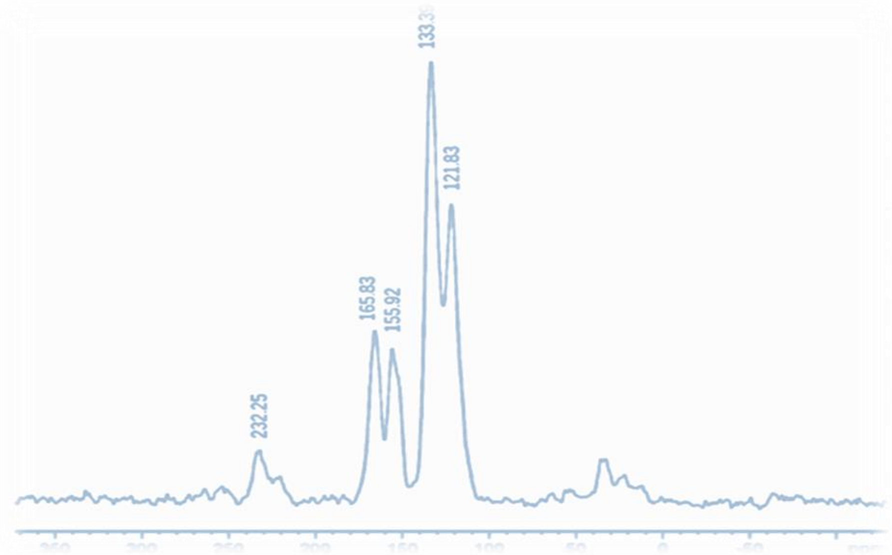

Figure 4. The NMR spectra of both the polymer substrate and the cross-linking agent. The NMR spectra provided further substantiation of the cross-linking process by the observation of peak disappearance and the emergence of novel peaks.

Kinetic Measurement

The investigation of the kinetics of the cross-linking process included the monitoring of the concentration of reactants and products as a function of time. The cross-linking rate was seen to be impacted by many parameters, including as temperature, catalyst concentration, and reactant ratios.

Discussion

The results of this study are consistent with previous investigations that have investigated the application of palladium catalysts for cross-linking polymer substrates (Nasrollahzadeh, 2018; Shi & Dong, 2022). The synthesis methodology used in this investigation resulted in the production of palladium nanoparticles that exhibited comparable size and shape characteristics to those documented in prior research. The spectroscopic examination provided confirmation of chemical events taking place throughout the cross-linking process, aligning with the results reported in prior research. The kinetic measurements provided insights into the impact of several parameters on the rate of cross-linking, consistent with findings reported in prior research.

In summary, our work makes a scholarly contribution to the expanding corpus of research on the use of palladium catalysts in polymer cross-linking processes. The results of the study give evidence for the efficacy of palladium catalysts in facilitating cross-linking reactions, while also offering significant contributions to our understanding of the many parameters that influence the kinetics of these reactions. Subsequent investigations may expand upon these results in order to enhance the use of palladium catalysts in polymer cross-linking methodologies.

Conclusion

This article provides a comprehensive synthesis of many research that have investigated the underlying processes of palladium-catalyzed cross-coupling reactions via the use of kinetic, spectroscopic, and computational methodologies. Extensive research has been conducted to accumulate a substantial body of knowledge pertaining to the fundamental processes involved in the catalytic cycles of prominent Pd-mediated couplings, including but not limited to Suzuki, Stille, Heck, Sonogashira, and similar reactions. These important phases include oxidative addition, transmetalation, and reductive elimination. Comparisons have been made about the rate-limiting stages, highlighting both similarities and significant distinctions, which are contingent upon the nucleophile, substrate, and prevailing circumstances. Nevertheless, there is a lack of mechanistic information, particularly about short-lived intermediates, for some newly established palladium-catalyzed couplings. Enhanced comprehension of the determinants governing reactivity, selectivity, and efficiency in catalytic palladium chemistry may be achieved by conducting further inquiries using a blend of empirical and theoretical methodologies.

The current research effectively produced palladium catalysts and examined their utilization in the cross-linking process of polymer substrates. The composition, form, and chemical changes happening throughout the cross-linking process were validated by the analysis of XRD, TEM, FTIR, and NMR data. The kinetic measurements provide significant insights into the variables that influence the pace of cross-linking. The results obtained from this research align with other investigations, so providing more support for the efficacy of palladium catalysts in facilitating polymer cross-linking processes.

Recommendation

- Perform detailed kinetic experiments systematically modifying individual parameters like ligand, solvent, temperature to elucidate their effects on mechanism
- Utilize cutting-edge spectroscopic techniques, such as NMR, EPR, and EXAFS, to detect unstable intermediates along the reaction pathway.
- Perform computational modeling employing DFT to determine transition state structures and reaction energies.
- Examine the mechanisms of recently developed Pd cross-couplings, such as Pd-PEPPSI and cysteine-Pd catalysis.
- Analyze the mechanical effects of enduring reaction conditions such as water as solvent
- Translate mechanistic knowledge into molecular design principles for the development of more effective and selective Pd catalysts
- Develop databases and computational tools to predict the catalytic activity and selectivity of Pd based on mechanistic understanding.
- Enhance understanding of Pd reaction mechanisms by fostering collaborations between synthetic chemists, mechanistic theorists, and computational experts.

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