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CHEM 4420 Literature Review

Pd-PEPPSI Catalysis in Suzuki-Miyaura Cross-Coupling of Amides

Transition-metal-catalyzed cross-coupling reactions have become fundamental in modern organic synthesis, providing efficient methods for forming carbon-carbon and carbon-heteroatom bonds. One of the most well-established examples is the Suzuki-Miyaura cross-coupling reaction, which is widely used for the formation of biaryl compounds and has been employed in our course experiments using boronic acid, bromobenzene, and tetrakis(triphenylphosphine)-palladium(0) ($Pd(PPh_3)_4$) as a catalyst. While this reaction is traditionally applied to aryl halides, recent advances have expanded its scope to include amide bond activation, which has remained a significant challenge due to the strong resonance stabilization of the C–N bond. This stabilization makes it highly resistant to cleavage under typical reaction conditions and reduces the efficiency of oxidative addition.[1] Previously, traditional phosphine-ligated palladium ($Pd\text{-}PR_3$) catalysts have been widely used in cross-coupling reactions, but they often require high reaction temperatures and rigorous air-free conditions due to their sensitivity to moisture and oxygen[1,2]. Nickel-based catalysts have been explored as an alternative, but they exhibit lower functional group tolerance, making them less practical for certain applications.[3,4] These limitations highlight the need for a more robust catalytic system that can activate amide bonds under mild conditions without compromising efficiency or substrate scope.

Lei et al. address this challenge by investigating palladium pyridine-enhanced precatalyst preparation stabilization and initiation (Pd-PEPPSI) with an isopropyl (IPr) N-heterocyclic carbene (NHC) ligand as a precatalyst for Suzuki-Miyaura cross-coupling.[5] Previous studies have demonstrated the effectiveness of Pd-NHC catalysts in cross-coupling reactions, showing their strong σ-donating properties and ability to facilitate oxidative addition.[6] Given these advantages, the researchers chose to explore Pd-PEPPSI-IPr, which is known for its high reactivity and air- and moisture-stability. Their goal was to develop a catalytic system capable of operating under milder conditions while maintaining a broad substrate scope. By expanding the range of amide substrates that can undergo cross-coupling, this work has significant implications for pharmaceutical synthesis and the construction of complex organic molecules.

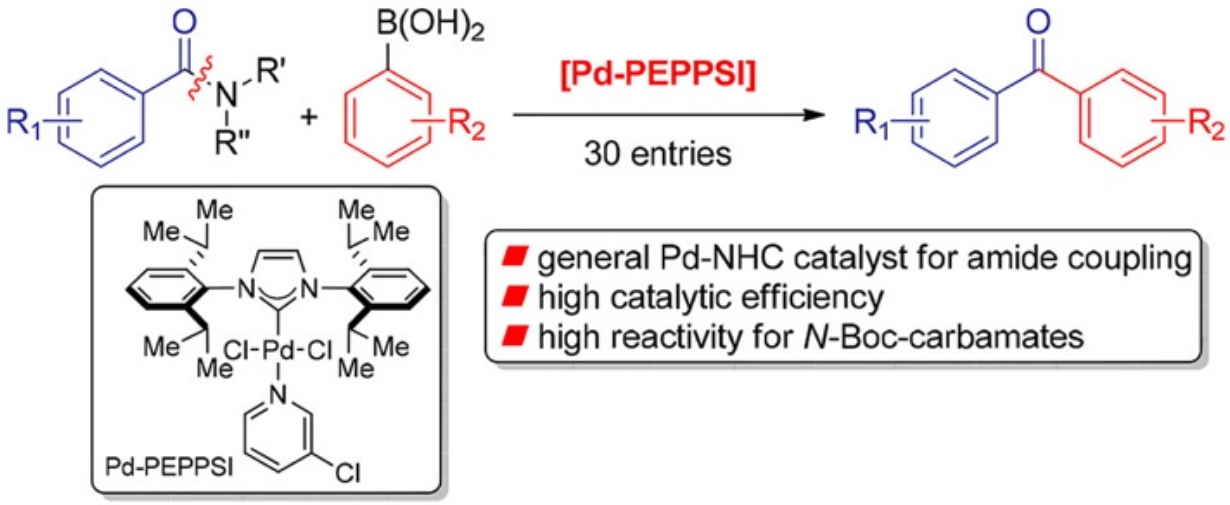

Figure 1. Graphical Abstract of PD-PEPPSI Catalysis for Efficient Suzuki-Miyaura Cross-Coupling of Amides

As summarized in Figure 1, the study utilizes Pd-PEPPSI-IPr, a well-defined palladium-NHC complex, as the precatalyst. This complex is known for its exceptional air and moisture stability, making it significantly easier to handle compared to conventional Pd-PR_3 catalysts. The

researchers evaluate the effectiveness of Pd-PEPPSI-IPr across a range of amide substrates, including N-acyl-*tert*-butyl-carbamates (N-Boc), N-acyl-tosylamides (N-Ts), and N-glutarimide amides, which are chosen due to their ability to undergo selective C–N. Arylboronic acids serve as the coupling partners, while bases such as potassium carbonate (K_2CO_3), potassium fluoride (KF), and tripotassium phosphate (K_3PO_4) were tested to optimize reaction conditions. The reactions were conducted in tetrahydrofuran (THF) for most of the reactions, though dioxane and toluene were also explored but had worse yield. They also carried out the reactions at temperatures ranging from 60°C to 80°C to assess the impact of temperature on the reaction. A mechanistic investigation further determined how Pd-PEPPSI-IPr facilitates oxidative addition into the amide bond and how its activation mechanism differs from other Pd-NHC catalysts like (NHC)Pd(R-allyl)Cl. Through optimization, this study focuses on how solvent choice, base selection, and reaction temperature impact catalytic efficiency, providing a comprehensive evaluation of the system.

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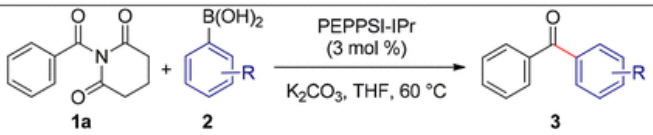
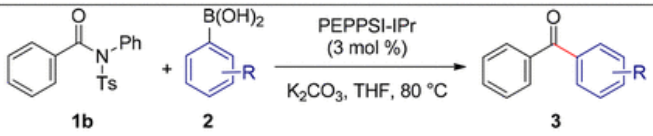
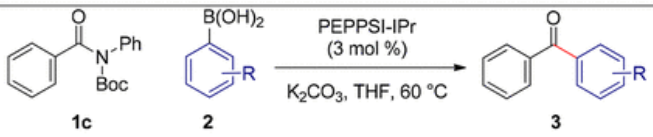
Figure 1. Pd-PEPPSI-Catalyzed Suzuki-Miyaura Cross-Coupling of Amides and Boronic Acids

entry	amide (Ar_1)	Ar_2-$B(OH)_2$	yield (%)
	 **1a** **2** **3**		
1	Ph	R = H	94
2	Ph	R = 2-CH_3	97
3	Ph	R = 4-CH_3	97
4	Ph	R = 4-OMe	98
5	Ph	R = 4-CO_2Me	90
entry	amide	Ar-$B(OH)_2$	yield (%)
	 **1b** **2** **3**		
6	Ph	R = H	92
7	Ph	R = 2-CH_3	83
8	Ph	R = 4-CH_3	83
9	Ph	R = 4-OMe	85[c]
10	Ph	R = 4-CO_2Me	63[c]
entry	amide	Ar-$B(OH)_2$	yield (%)
	 **1c** **2** **3**		
11	Ph	R = H	94
12	Ph	R = 2-CH_3	90
13	Ph	R = 4-CH_3	92
14	Ph	R = 4-OMe	98
15	Ph	R = 4-CO_2Me	90

The results of this study, as shown in Table 1, demonstrate that Pd-PEPPSI-IPr enables efficient Suzuki-Miyaura cross-coupling of amides under notably milder conditions than previous catalytic systems. The N-glutarimide and N-Boc reactions had a percent yield ranging from 90-98%, while the N-Ts reactions had 63-92% yield, although the lower yield for entry 10 is due to the requirement of 110 °C for efficient coupling between the amide and the arylboronic acid. One of the key advantages of this catalyst is its high reactivity and long-term stability, allowing for reproducible results without the need for stringent handling procedures. Importantly, Pd-PEPPSI-IPr exhibits broad substrate compatibility, showing particularly high reactivity with N-Boc amides, which are widely used in synthetic chemistry due to their ease of preparation and functional group tolerance. The unique activation mechanism of Pd-PEPPSI-IPr provides new insights into how ligand design influences catalytic performance, offering potential avenues for further catalyst development. The optimized reaction conditions—particularly the use of THF as a solvent and K_2CO_3 as a base—were found to contribute to high product yields and increased efficiency at temperatures as low as 60 °C.

Overall, this study presents a strong case for Pd-PEPPSI-IPr as a highly efficient and practical catalyst for the Suzuki-Miyaura cross-coupling of amides. Its improved stability, broad substrate scope, and ability to operate under milder conditions make it a valuable alternative to existing catalytic systems. These findings have significant implications for organic synthesis, particularly in pharmaceutical and fine chemical production, where robust and scalable catalytic methods are beneficial.

This study also builds on the concepts explored in our course's Suzuki-Miyaura cross-coupling experiment, where we used $Pd(PPh_3)_4$ to couple boronic acid with bromobenzene. While $Pd(PPh_3)_4$ is effective, its air sensitivity and need for stringent reaction conditions contrast with the air- and moisture-stable nature of Pd-PEPPSI-IPr. The mechanistic differences between these two catalysts highlight the importance of ligand choice in determining catalytic stability and efficiency. Additionally, our course experiment focused on aryl halide activation, whereas this study extends Suzuki-Miyaura cross-coupling to amides, demonstrating the adaptability of this reaction.

Future research should explore further ligand modifications to fine-tune catalytic performance and extend the range of amide substrates that can undergo cross-coupling. Additionally, investigating how different NHC ligand structures may affect reactivity could provide further insights into the fundamental principles governing Pd-PEPPSI catalysis. Continued optimization and mechanistic studies may unlock even broader applications for Pd-PEPPSI-IPr in modern synthetic chemistry.

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