

Pnictogens: Alternatives to metal-catalyzed cross-coupling

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Metal-catalyzed cross-coupling reactions are a cornerstone in synthetic chemistry. In the past three decades, chemists have utilized a variety of these reactions to assemble complex molecules such as natural products, medically relevant compounds, and materials.¹ Some notable examples of these cross-coupling reactions are the Buchwald-Hartwig amination and the Chan-Lam coupling (Figure 1). These reactions are very important since C-N bond formation is one of the holy grails within pharmaceutical R&D synthetic methodology development. The Buchwald-Hartwig is one of the most extensively used synthetic transformations in medicinal chemistry accounting for about 10% of the medicinal chemistry papers in 2014.² Both groups have extensively studied the mechanism of this reaction to increase the efficiency of oxidative addition and reductive elimination while preventing undesired reactions such as the β -hydride elimination. Understanding some of the fundamental factors governing this reaction improved catalyst design and the scope of the reaction. The Chan-Lam coupling is an alternative method for C-N bond formation. However, the mechanism of this reaction remains underdeveloped due to the multiple roles of the Cu catalyst and the multiple speciations of the Cu complexes.³

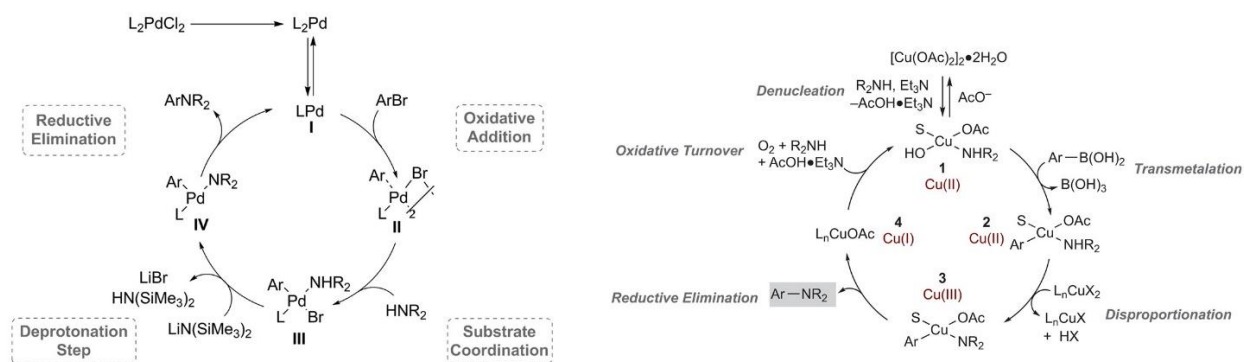


Figure 1. Buchwald-Hartwig C-N bond formation on the left and Chan-lam cross-coupling on the right

The use of transition metals specifically heavier elements poses a few problems in terms of the cost and the environmental issues associated with mining and toxicity. Finding alternative ways to perform the same cross-coupling reactions using main group elements may be a more sustainable solution.

To this end, in 2020, Radosevich et.al reported a new catalyst 1,2,2,3,4,4 - hexamethylphosphetane oxide that is capable of doing C-N bond formation in the presence of a suitable reductant such as phenyl silane ($PhSiH_3$).⁴ Imposing geometric constraints onto the phosphorus center enables biphilic reactivity and their use as transition metal-free catalysts.⁵ The authors first optimized the reaction conditions in terms of catalyst loading, solvent, and reductant

equivalences. Solvents of moderate polarities such as cyclopentyl methyl ether (CPME) and dichlorobenzene (DCB) were found to be superior for this transformation. Low catalyst loading at 2 mol% can be used but that results in longer reaction times. Detailed mechanistic studies were performed to probe the mechanism of the reaction and assess whether any undesired reactions were occurring. Rate data, Hammett plot parameters, and DFT calculations gave some insight into the mechanism of the reaction. The turnover-limiting cycle involves deoxygenating the nitro group forming a nitroso phenyl that subsequently reacts with the catalyst through a series of steps to give the desired product (Figure 2). Through a series of competition experiments, the authors determined that undesired products could be avoided by carefully selecting the correct combination of solvent and reductant.

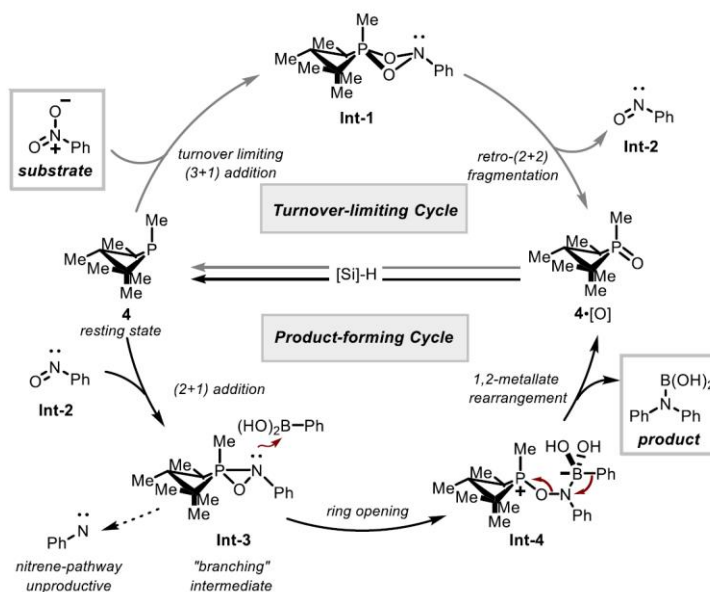


Figure 2. Catalytic cycle for C-N bond formation

In an earlier study, Radosevich et.al reported the use of the same catalyst for iterative C-N followed by C-C cross-coupling reactions.⁶ To orchestrate these series of bond formations, the oxidant and reductant must be compatible. Diethylbromomalonate and phenyl silane were chosen as the oxidant and reductant respectively. The catalyst facilitates the formation of an amide bond followed by cyclization/dehydration to afford complex molecules. The substrate scope included some remarkable molecules such as the Jansen antifungal agent that is synthesized in one step using a single catalyst. There were some mechanistic studies performed using ¹H NMR and ³¹P NMR. However, this study lacked computational work to support the proposed mechanism.

In 2020, Cornella et.al reported a bismuth catalyst that can facilitate the oxidative fluorination of boronic acids.⁷ As we move down the periodic table, relativistic effects dominate electronics causing Bismuth to be oxidizing.⁵ The smart ligand design included a sulphone group with lone pairs that stabilize the high valent Bi center. Moreover, the electron-withdrawing nature of this group would make the bismuth center more prone to reductive elimination. Simply substituting one of the oxygens in the sulphone group to NCF₃ leads to a drastic change in the oxidative addition product. In this study, the authors were able to find a mild oxidizing agent

which was dichloropyridinium tetrafluoroborate which offers an alternative to harsher oxidizing agents such as XeF₂ and F₂. The mechanism of reductive elimination was investigated, and it was determined that there is a cationic intermediate involved. Multiple boronic acids and esters were compatible with transmetallation.

In summary, these new catalysts based on Phosphorus and Bismuth provide alternatives for metal-catalyzed cross-coupling reactions. These catalysts were found to give high yields of desired products. The mechanistic investigations provide valuable insights to develop new catalysts that are based on main group elements.

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