Expert Article

ADVANCES IN PALLADIUM CATALYST TECHNOLOGY FOR **CROSS-COUPLING REACTIONS**

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Advances in palladium catalyst technology for **cross-coupling reactions**

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Few reactions are as essential to the modern chemical industry as cross-coupling. As a synthetic tool, it provides a reliable and flexible route to a plethora of organic compounds. This is especially true for the pharmaceuticals industry, where cross-coupling reactions have made an impressive impact across drug discovery, development and manufacturing, facilitating the production of both key intermediates and APIs at scale.

The prevalence of cross-coupling reactions within the pharmaceutical industry is due to the need for versatile, reliable and efficient tools for organic synthesis. However, without catalysts, their impact within industrial settings would be limited.

Palladium catalysts, such as those used in Suzuki couplings and Buchwald-Hartwig reactions, play a pivotal role in pharmaceutical manufacturing, enabling synthesis at much lower temperatures and pressures. This not only reduces energy consumption, but also removes the need for specialist equipment that can withstand harsh reaction conditions and widens the scope of cross-coupling to include less stable functional groups.

Cross-coupling catalysts can also improve the economic viability of chemical synthesis. By shortening the required synthesis pathway, less energy and solvent are required thereby reducing waste and cost. Platinum group metal catalysts also improve the selectivity of many reactions, helping to minimise the formation of side products. This is particularly important in later steps of synthesis, where high-cost waste can significantly impact process feasibility for industry.

Figure 1 – Umicore's closed-loop approach

Although palladium catalysts are well-established and effective at catalysing cross-coupling reactions, scientists still face some further challenges. With an increasing focus on greener industrial processes, they are continuing to develop new catalysts, to improve efficiency and discover the untapped potential for further synthetic opportunities.

Current challenges of cross-coupling catalysis

Over the last 70 years, our understanding of cross-coupling has grown, with scientists adapting the mechanism to work for a wide range of reactions. As such, a wide variety of palladium-based catalysts are available today. However, it is not always obvious or easy to select the correct catalyst for a specific reaction.

Another important consideration to make when choosing palladium catalysts is the downstream processing required to separate the catalyst from the final product, which demands additional manufacturing steps and can result in higher costs. Under current legislation, the residual metal must be <10 ppm. This is especially important in pharmaceutical production to ensure patient safety.

With an increasing focus on the environmental impact of cross-coupling reactions, chemists are faced with the challenge of synthesising more complex targets in fewer steps and minimising the use of scarce resources such as precious metals such as palladium, as well as reducing energy consumption and waste.

Overcoming the challenges

Pharmaceutical development is a multi-faceted process, requiring strong collaboration throughout the pipeline to co-create innovative and cost-effective solutions. A good catalyst supplier will work collaboratively to advise on palladium catalyst selection, considering both activity and selectivity for maximised yield, as well as optimised loading.

Downstream processing and catalyst separation is important for ensuring the quality of the finished product. Further, this step provides processors with an opportunity to consider a circular and more sustainable closed-loop

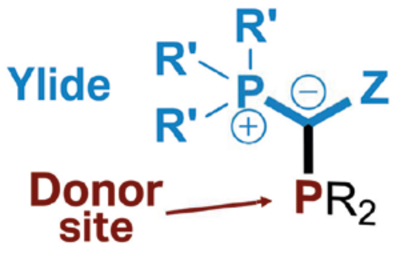

Figure 2 - General structure of a YPhos ligand

Note: *Where an aryl or alkyl substituent would normally be expected is the phosphine ligand as an ylide group (coloured blue)*

approach to catalyst lifecycles. Closed-loop systems like Umicore's (Figure 1) offer an economic advantage, as the cost of recovering and processing existing palladium is lower than mining the metal.

Additionally, by using 100% recovered palladium, companies can avoid the use of conflict material. By working closely with supply chain partners, manufacturers can implement effective precious metal recovery programmes, preserving scarce raw materials. And, as up to 80% of precious metal value can be recovered, this reduces future catalyst spend.

Identifying ideal properties

In order to design and develop innovative and improved palladium catalysts, the target properties for cross-coupling catalysis must first be understood. Firstly, the efficiency of the catalyst can be measured by the turnover number (TON), the number of moles of substrate that a mole of catalyst can convert before becoming inactivated. The higher the TON, the more efficient the catalyst.

Catalysts should also endeavour to optimise the reaction conditions – ideally as close to room temperature and pressure as possible. Finally, a good catalyst will be relatively stable for reduced complexity in storage and handling.

Precious metal catalysis design is highly dependent on ligand selection. Ligands significantly impact the activation energy of a catalytic reaction, determining the temperature and pressure under which a reaction will occur. They also influence the selectivity of the reaction, improve the solubility of metal catalysts in organic solvents for extraction and extend catalyst lifetimes by reducing the impact of degradation pathways.

Generally, the ligands chosen when designing palladium cross-coupling catalysts are sterically bulky and electron-rich. Sterically bulky ligands have two major advantages: they have increased selectivity, due to limited access to the metal centre, and provide additional structural support to the catalyst. Ligands that are electron-rich increase the nucleophilicity of the palladium core, which in turn lowers the activation energy required for cross-coupling reactions.

Recent advances

In any industry manufacturers are constantly looking to improve sustainability, increase profit margins and alleviate time pressures. Focusing on the pharmaceutical pipeline, catalyst providers can support these goals by reanalysing traditional approaches and developing new solutions with green chemistry principles in mind.

One way in which researchers are looking to optimise cross-coupling catalysis is by improving the ligands within the catalytic systems. Brad Carrow's group at Princeton University, US, synthesised tris(1-adamantyl) phosphine (PAd_3). They found that, when associated with a palladium core, PAd_3 complexes catalyse Suzuki couplings with an exceptional TON of close to 20,000.[1]

The high efficiency demonstrated by the palladium complexes of these new phosphines allow for shorter reaction times, even without increasing the temperature of the reaction vessel. This enables a temperature range with higher flexibility for chemists to work within, thus allowing the reaction to be run at room temperature.

With milder conditions, the reaction now has increased compatibility with temperature-sensitive functional groups, which opens new greener syntheses for existing reactions and potential new pathways to form new products – making the PAd^3 ligand a powerful tool for research chemists.

Additionally, recent work by Viktoria Gessner's group at Ruhr University Bochum, Germany, showed how an understanding of structure-activity relationships, steric demands, and donor properties, can lead to more effective cross-coupling catalysis. By exploring new ligand structures and arrangements, Gessner and co-workers have discovered a class of ylide-containing phosphines they have termed the YPhos* family (Figure 2).

The ylide substituent provides strong electron-donating properties to the phosphorus donor site. The electron-richness of the YPhos contributes to a uniquely high activity in cross-coupling reactions, especially Buchwald-Hartwig aminations. Additionally, while ylides are known to be a highly reactive species, YPhos ligands tend to be stable when complexed with a metal, owing to additional reactions between the ligand and the metal species.

Outlook

As a universal tool in the pharma and fine chemical industry, the advance of palladium cross-coupling catalysis has the potential to create a real impact on the sustainability of pharmaceutical synthesis. As such, R&D teams are now leveraging the comprehensive understanding of this established field to design new, more efficient catalysts.

However, collaboration between academia, manufacturers and the wider supply chain will be vital as the pharmaceutical industry looks to enable greener drug discovery, development and manufacture. Considerations such as downstream processing and precious metal recovery are important areas for collaboration, to move towards a more circular and sustainable economy. ●

**YPhos is a registered trademark of Umicore*

References:

1: *J. Am. Chem. Soc. 2016, 138, 20, 6392–6395; https://doi.org/10.1021/jacs.6b03215*

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