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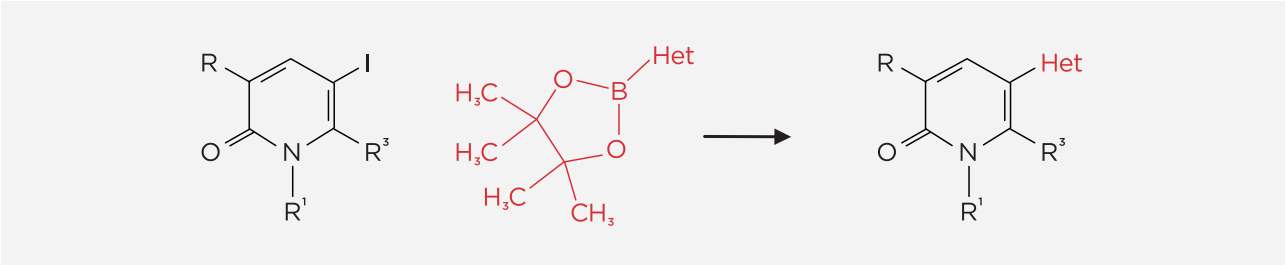
# Case Study: Ligand Selection for a Suzuki Reaction

This Suzuki reaction was developed to deliver a late stage intermediate in the synthesis of a pharmaceutical API. The reaction performed successfully on scale to deliver 40kg of API for clinical development. The reaction used a relatively high loading of the air stable and reactive palladium (II) catalyst, 1,1 -Bis(di-tert-butylphosphino)ferrocene dichloropalladium.




The project was moving to final scale-up prior to commercial manufacture and the catalyst cost was as the most significant factor to address. It was estimated that the catalyst cost to deliver 100kg of API was in the region of $500,000.

During the development process, decomposition of the boronic acid was observed in slower reactions and therefore, a high catalyst loading was maintained to minimise decomposition of expensive intermediates. The objective of this study was to identify an alternative catalyst to reduce the cost of the process while maintaining high chemical purity and reducing the palladium content of the process.

## Objective: To identify alternative catalyst systems to provide the required material in high purity at lower overall cost.

A Design of Experiments (DoE) of 32 experiments plus 6 controls was undertaken to investigate 18 ligands plus 2 palladium salts.

The selected ligands included monodentate and bidentate phosphine's, which were chosen from their respective Principal Component Analysis (PCA) maps. Both maps have three principal properties (3 dimensions) to explain more than 70% of the variance of the dataset and separate designs were created for each ligand selection. The reaction procedure was modified and the DoE executed. Both monodentate and bidentate ligands were found to be successful in the reaction. The results of the DoE identified that 3 ligands performed as well or better than the initial catalyst. These are seen in Figure 2 (dark green).

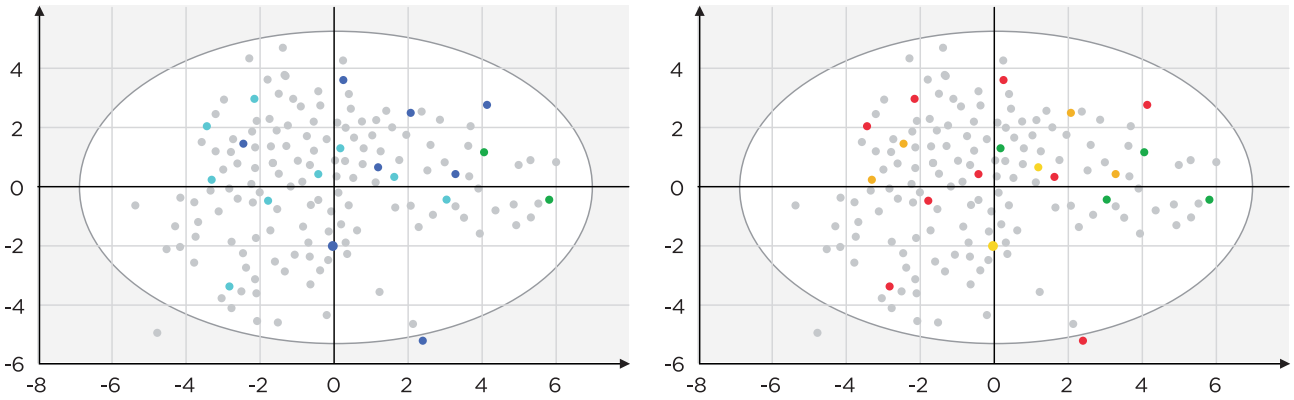



Figure 1 shows a diverse selection of ligands. Figure 2 shows results from initial screen

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Analysis of the results from the initial screening identifies a wider region of ligand activity. The plot in figure 2 is of principal components 1 and 2. Subsequent principal components separate the unsuccessful ligands in the region of activity. Additional ligands were selected to probe the region around the 'sweet spot' of activity. Two iteration of additional selections were made identifying additional suitable ligands (Figure 3 and 4).

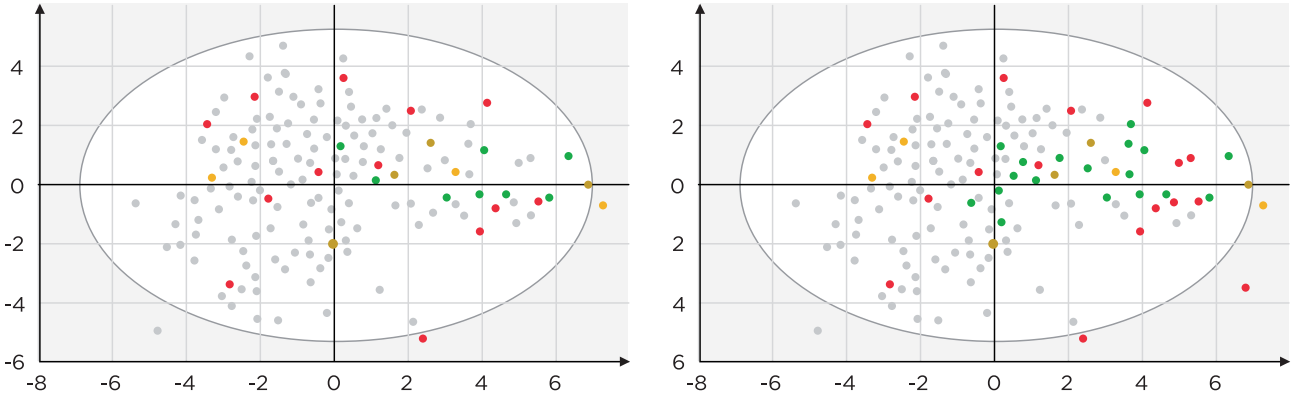


Figure 3 shows additional ligands identified. Figure 4 shows further ligand selection defining active region

Ligand screening using PCA identified a number of alternative ligands. The modified experimental procedure enabled a greater than 5 fold reduction in the catalyst loading while providing a more robust process. Alternative catalysts such as $^{t}Bu_3P.HBF_4$ / $Pd(OAc)_2$ offered a reduction in catalyst and ligand cost of approximately 5 fold with similar reactivity. The modified procedure allowed the use of less active ligands and $PPh_3$ has been shown to be a viable ligand for this reaction, but with a longer reaction time.

In summary the use of PCA and DoE to explore alternative catalysts and ligands for this Suzuki reaction identified a number of alternative catalytic systems with a potential to reduce the catalyst costs for the process by more than $400,000. The use of PCA allowed informed rational decision making and provided a better more robust process.



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