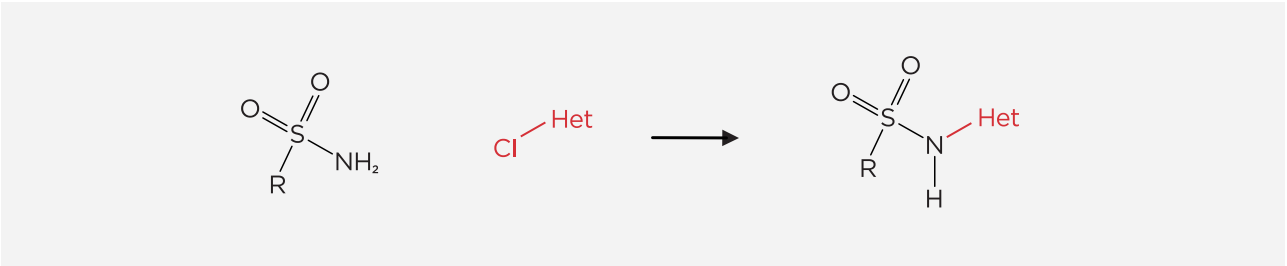
CATALYSIS CONSULTING

Case Study: Ligand and Catalyst Selection for a Buchwald Hartwig Reaction

This Buchwald Hartwig reaction was developed to deliver an intermediate in the synthesis of an Active Pharmaceutical Ingredient (API). The reaction performed successfully to deliver 25 kg of API for clinical development. The reaction used XPhos with Pd_2dba_3.



The project was using XPhos which at the time was costing approximately $20,000 per kg and thus interested in identifying an alternative cheaper ligand. A secondary objective of the project was to replace Pd_2dba_3 with a more stable and less expensive catalyst. It was estimated that the catalyst and ligand cost to deliver the next 80 kg of API was in the region of $300,000.

Objective: To identify alternative catalyst systems to provide material with the required? at lower overall cost.

A Design of Experiments (DoE) utilising 20 ligands and 2 palladium salts was constructed to investigate the effects of ligands and palladium precursors. The selected ligands included a diverse range of 9 monodentate and 9 bidentate phosphines along with XPhos and CataCXium PCy as controls as shown in Figure 1. The ligands were chosen from their respective Principal Component Analysis (PCA) maps. Both maps have three principal components to explain more than 70% of the variance of the dataset and separate designs were created for each ligand selection. An initial run of 32 experiments plus 6 controls was completed.

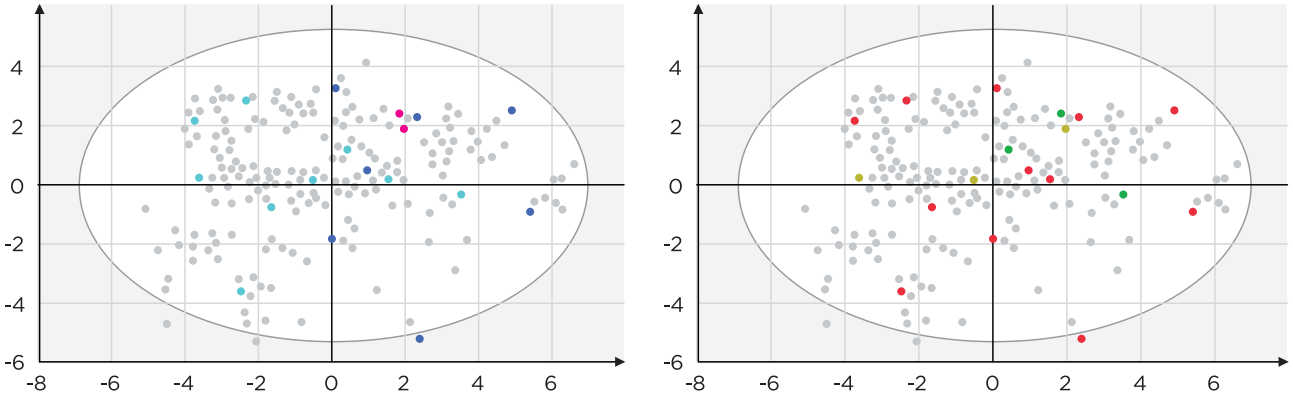


Figure 1 shows a diverse selection of ligands. Figure 2 shows results from initial screen

The results of the DoE showed that apart from XPhos, only bidentate ligands were found to be successful in the reaction. Palladium acetate was also shown to be as successful as the original catalyst. The results of the DoE immediately identified 2 new ligands which performed as well as XPhos. These are seen in Figure 2 in dark green).

Analysis of the results from the initial screening identified a wider region of ligand activity. The plot in Figure 2 is of principal components 1 and 2. Additional 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 iterations of additional selections were made identifying additional suitable ligands (Figures 3 and 4).

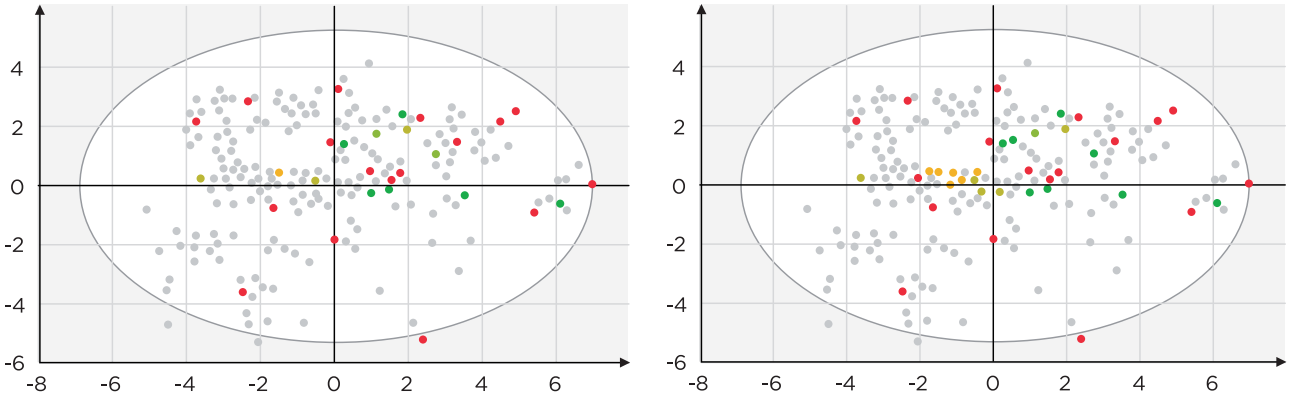


Figure 3 shows additional ligands identified. Figure 4 shows further ligand selection defining active region

One of the ligands near the optimal region, DPEphos, gave an 80% conversion after 24hrs, compared to full conversion in 3hrs with XPhos. This ligand is much cheaper than XPhos, estimated at $500 per kg. A subsequent experimental design was carried out to optimise DPEphos looking at the following parameters: metal source, metal mol%, ligand to metal ratio, temperature and equivalents of reagents. A DoE of 16 experiments plus 6 controls was carried out. The results of the DoE showed optimal conversion of the starting materials was achievable in 3hrs (Figure 5) with the same catalyst loading providing material of the required quality.

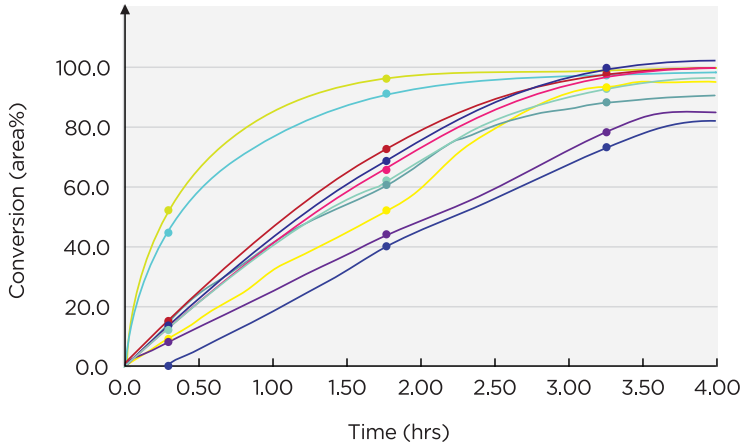


Figure 5 shows reaction profiles for DoE: optimisation of DPEphos

In summary the use of PCA and DoE to explore alternative catalysts and ligands for this Buchwald Hartwig reaction identified a number of alternative catalytic systems with a potential to reduce the costs for the process to a 14th of the original cost, a saving of $280,000. The use of PCA allowed informed rational decision making and provided a more cost effective process.

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