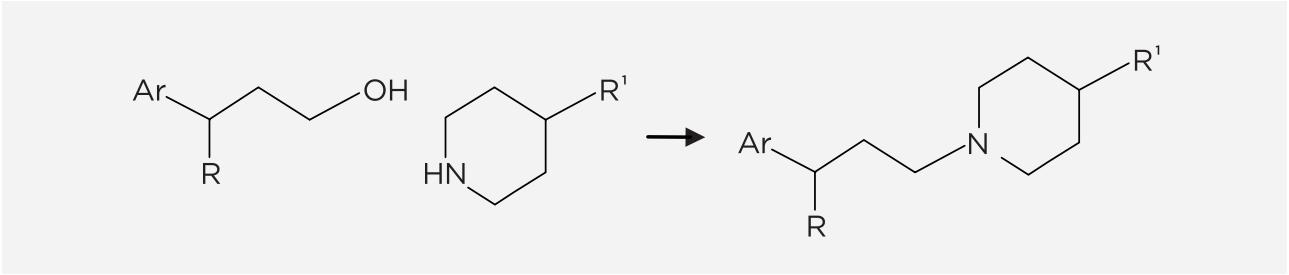
CATALYSIS CONSULTING

Case Study: Ligand and Catalyst Selection for a Redox-Neutral Alcohol-Amine Coupling

This Redox-Neutral Alcohol-Amine Coupling reaction was developed as an alternative synthesis of an Active Pharmaceutical Ingredient (API) replacing the S_N2 displacement of a tosylate.



The project under development in a major pharmaceutical company used a S_N2 reaction to generate a tertiary amine from a secondary amine and a tosylate as the final step to produce an API. The reaction generated levels of a dimeric impurity that was difficult to remove from the API. The potential use of the redox-neutral alcohol-amine coupling was seen as a safer route as it:

- Reduced the overall synthetic sequence by 1 step,
- Was unlikely to generate the troublesome dimer impurity, and
- Removed the use of tosyl chloride – an alkylating agent.

Objective: To identify an alternative synthesis without the use of potentially harmful alkylating agents.

A Design of Experiments (DoE) utilising 18 ligands, 9 solvents and 2 metal catalysts was constructed to rapidly assess the potential of this catalytic reaction. The selected ligands included a diverse range of 9 monodentate and 9 bidentate phosphines 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 64 experiments plus 6 controls was completed.

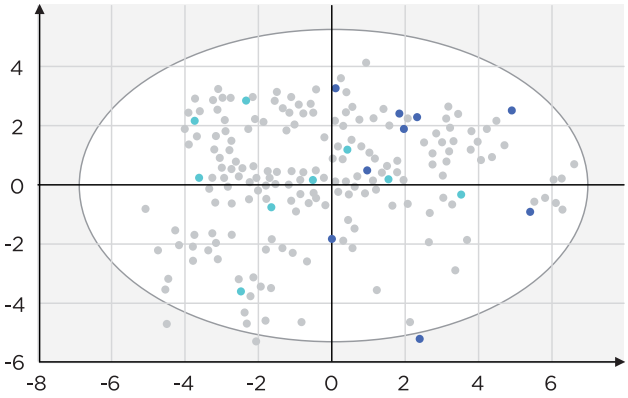


Figure 1 shows a diverse selection of ligands.

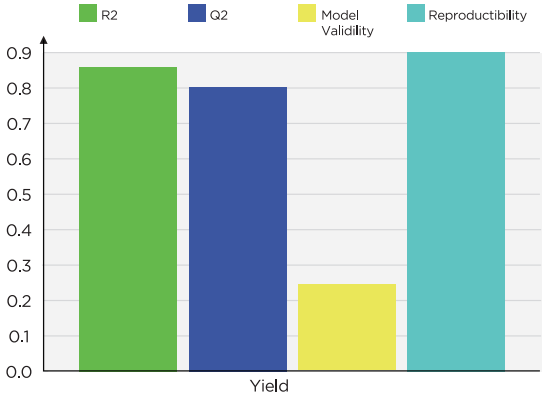


Figure 2 shows a Model Summary.

The reaction showed excellent conversion of starting materials to product in many reactions with minimal impurities providing an excellent model (Figure 2). Analysis of the experimental design showed that both the type of ligand and solvent were very important in the reaction because of their interactions (Figure 3). This experimental design enabled the accurate predictive of all the ligands in the database (Figure 4).

Paul Murray Catalysis Consulting Ltd • Company No. 08692613 • www.catalysisconsulting.co.uk
T +44 1454 325530 • M +44 7833 384027 • E paul.murray@catalysisconsulting.co.uk

Additional experiments were carried out to determine the minimum catalyst loading for this process. Reactions using a subset of the originally identified ligands showed that the catalyst loading could not be reduced below 5-mol% without significantly slowing or stalling the reactions.

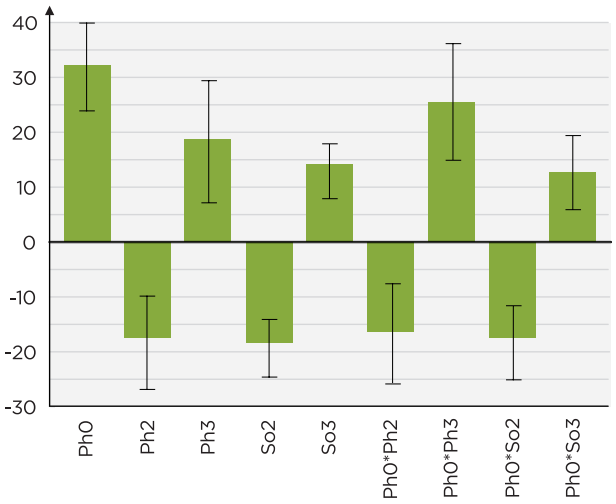


Figure 3 shows a Coefficients plot.

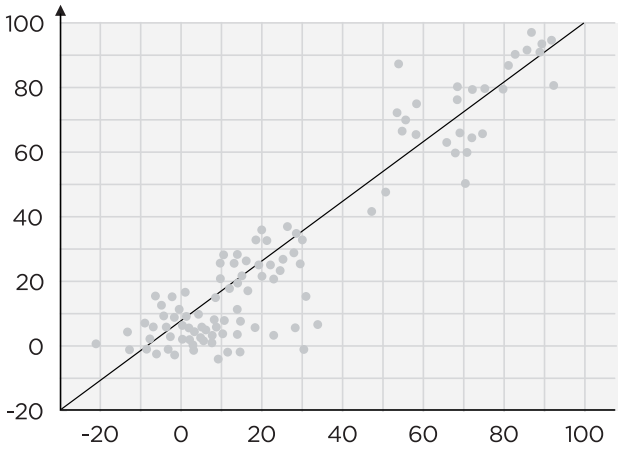


Figure 4 shows Model predictions.

In summary, the combination of DoE and PCA allowed the rapid assessment of an alternative catalytic system for a new API. An additional assessment showed that the reaction worked well but the required high catalyst loading made the reaction economically unviable. The whole process took less than 2 weeks to demonstrate the viability of the route and make a clear decision on the cost effectiveness of the reaction.

Paul Murray Catalysis Consulting provides Consulting and Training in Design of Experiments (DoE), Principal Component Analysis (PCA), homogeneous, heterogeneous and biocatalysis.

Paul Murray Catalysis Consulting Ltd • Company No. 08692613 • www.catalysisconsulting.co.uk
T +44 1454 325530 • M +44 7833 384027 • E paul.murray@catalysisconsulting.co.uk