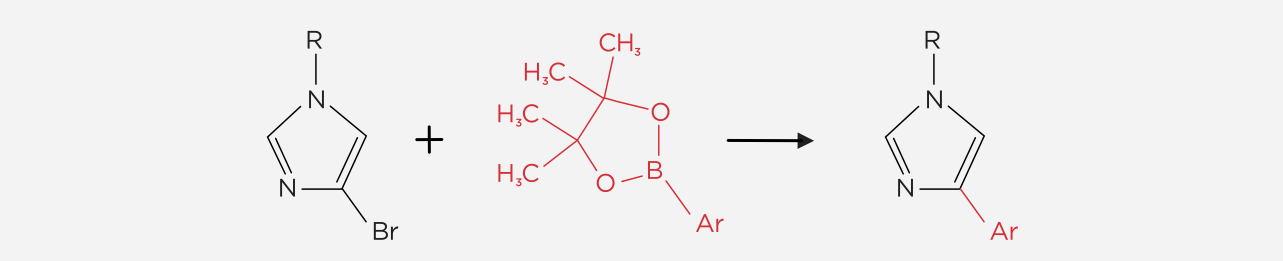
CATALYSIS CONSULTING

Case Study:
Base Effects in a Challenging Suzuki Reaction

This Suzuki reaction was developed to deliver an intermediate in the synthesis of an Active Pharmaceutical Ingredient (API). The reaction was low yielding (< 45%) with a very high catalyst loading. The reaction would not go to completion with significant starting material remaining when the reaction has stopped.

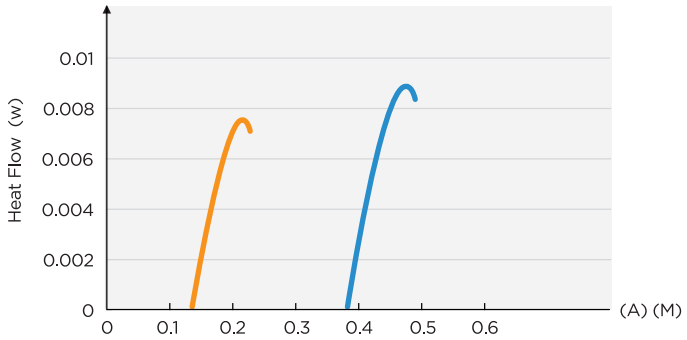


The project was looking to make 5 kg of the intermediate. The low yield, high catalyst charge, poor reproducibility and challenging workup were making the project delivery difficult.

Objective: To rapidly develop a reaction system to efficiently provide a high purity material.

Initial sighting experiments were carried out to look at solvent, ligand, base and water effects on the reaction. The use of a highly active catalyst system in a mixture of THF and water with potassium carbonate increased the conversion from < 45% to > 70%. However, the reaction still did not go to completion and there was significant amounts of the starting materials remaining in the solution.

To assess the prospect of catalyst poisoning a small number of additional experiments were carried out using the reaction progress kinetics decision tree. The reaction was studied with calorimetry where the catalyst loading was doubled. The addition of twice as much catalyst was expected to give a faster reaction with higher conversion if the catalyst was being poisoned, however, no increase in the rate was observed.



Calorimetry to investigate the rate of reaction at two different catalyst loadings

The calorimetry combined with mechanistic understanding pointed to a problem with the transmetallation of the aryl boronic ester in the reaction. A change of base from potassium carbonate to sodium hydroxide resulted in a complete clean conversion of both starting materials to afford the desired high purity product. The new cleaner reaction permitted a simple isolation by crystallisation. The whole study took approximately 1 week.

In summary, the understanding of reaction mechanism and kinetic evaluation for this Suzuki reaction identified a new, high yielding and robust process for the rapid delivery of 5 kg of the required API intermediate.

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