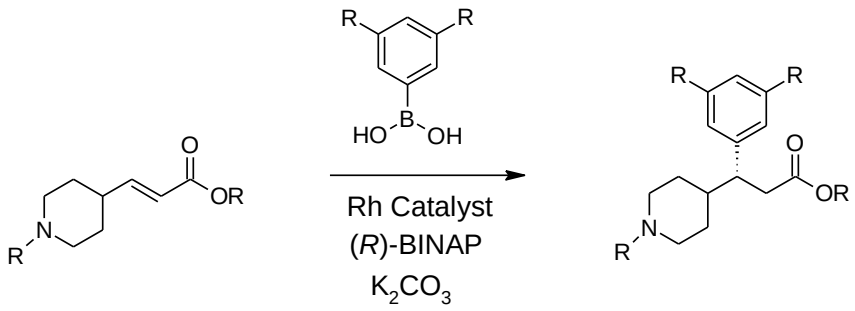
DoE is an extremely powerful tool when used properly with all sources of variation either being controlled or investigated. If you do not recognise the important factors in a reaction the investigation will be unreliable and this can lead to reproducibility and quality issues. Excessive variation in results is a sign that a factor is not being controlled and, if the designed experiments have been conducted properly, the results are telling you there is an uncontrolled factor you haven't thought of that is causing the variation.



A rhodium catalysed 1,4-addition reaction was developed to replace a Cu-catalysed reaction with a Grignard, which proved problematic on scale. The reaction gave good yields of >74% with a high e.e. on lab and pilot plant scale. Reaction optimisation showed that the catalyst could be reduced from 2 mol% to less than 0.1 mol% giving complete conversion and high stereoselectivity. The first signs of a reproducibility issue came during the preparation of a process for a larger campaign to supply material for phase 3 clinical trials. A user trial gave incomplete reaction after 24 h.

Objective: To identify the source of variation and prevent it.

In preparation for the new campaign fresh batches of the catalyst, ligand and all other components, were purchased from new suppliers. The failed use-test placed significant pressure on identifying the source of the problem so as to not delay the delivery. A DoE was carried out comparing the new and old batches of materials. All reactions in the DoE afforded full conversion and showed no problems with any of the new materials: the variation was not caused by the new chemicals.

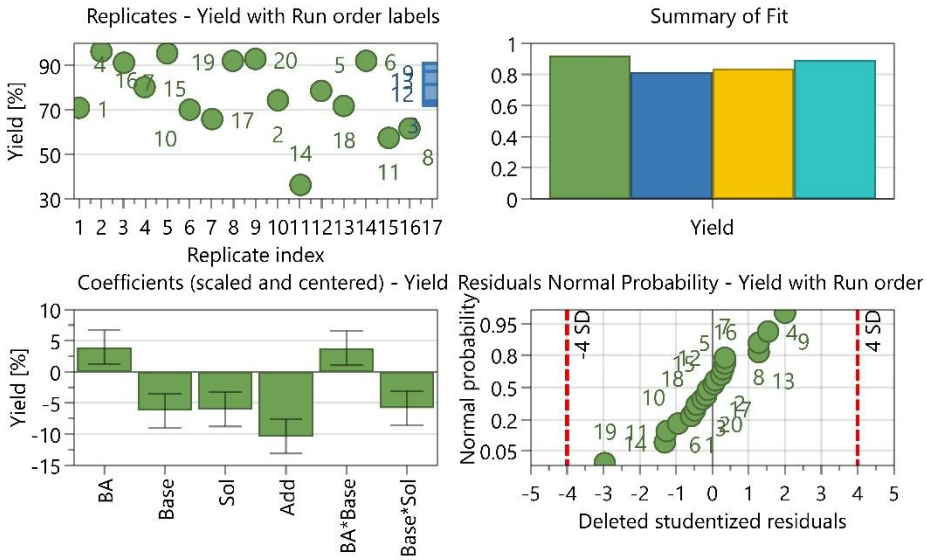


Figure 1: Model summary for the 1,4-addition with wide factor ranges

The pilot production went ahead on a 3000 L scale and behaved as expected. However, further lab work, even carried out in a glove box, started to routinely show incomplete reaction. Experimental designs carried out on a small scale initially showed a higher than desirable spread in the repeat experiment, but good models were generated from the data (Figure 2). Ideally, less than 5% variation is preferred between repeat experiments.

When the experimental designs were carried out in triplicate they showed extremely poor reproducibility with 5-70% variation (Figure 3). It was thought that all sources of variation were controlled as the reactions were carried out with degassed solvents in a glove box with automated addition and sampling but the designs showed otherwise. The problem was extremely hard to identify as the reaction was working on a large scale and had previously run without issue on smaller scales.

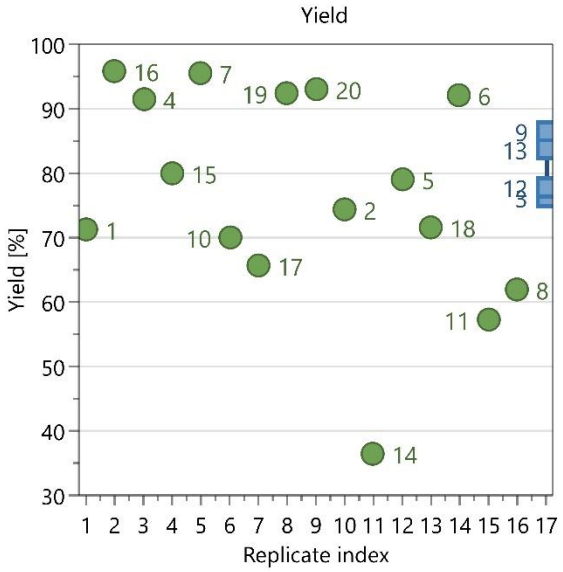


Figure 2: replicate plot for the initial design

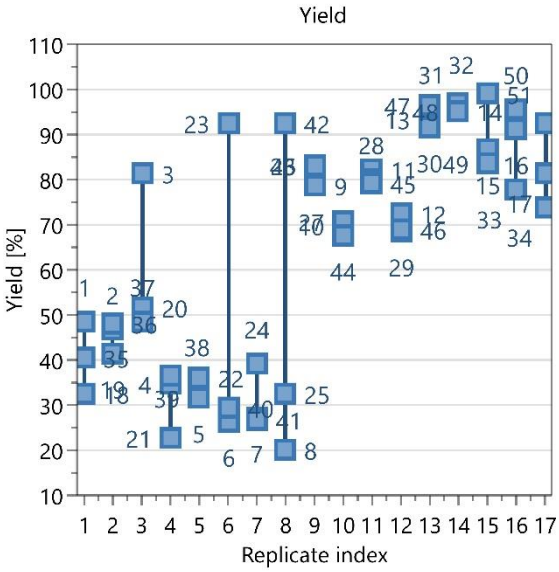


Figure 3: replicate plot for the design in triplicate

Eventually, after securing a specialist oxygen sensor from Mettler Toledo which could withstand THF at 50 °C, it was found that the level of degassing of the solvent was not as high as expected. The Rh-phosphine catalyst was found to be an oxygen scavenger and would immediately remove all oxygen from the solvent, generating an inactive catalyst. Additional attempts to degas the solvent by sparging with N_2 for several hours in the glove box, sonication and filtration were not rigorous enough. The only method which gave reliably degassed solvent was to reflux and cool back to room temperature under an N_2 atmosphere. When the solvent was subject to this treatment the reactions would behave as expected.

As we have observed in many examples, the problem could have been solved sooner if there had been an analytical technique to accurately study the suspected problem, rather than assuming a control was in place. Interestingly, the reaction was only problematic on the lab scale and reactions in the pilot plant continued without concern. It is thought that the inertion of the equipment train, and pumping of liquid through the N_2 atmosphere was resulting in the degassing of the solvent which could not be achieved on the lab scale.

DFT calculations were carried out comparing the $Rh(PMe)_3$ and $Pd(PMe)_3$ complexes. It was found that Rh has an oxygen affinity a hundred-fold that of Pd. The counter ion on the Rh (F^-, Cl^-, I^-, or OH^-) would affect how the oxygen behaved. In some cases it would bind to the Rh but in many others it instantly oxidised the ligand completely.

It is postulated that the lab solvents had changed, possibly coming from an alternative source, as can happen with the supply of material for laboratory use. Dissolved oxygen is not something typically found on certificate of analysis for materials and therefore would neither be analysed nor controlled. In this instance, DoE was useful in ruling out the reagent source and all other obvious factors as the source of variation. When the obvious factors are not the cause of the problem then expansion of the PSPs should be carried out.

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