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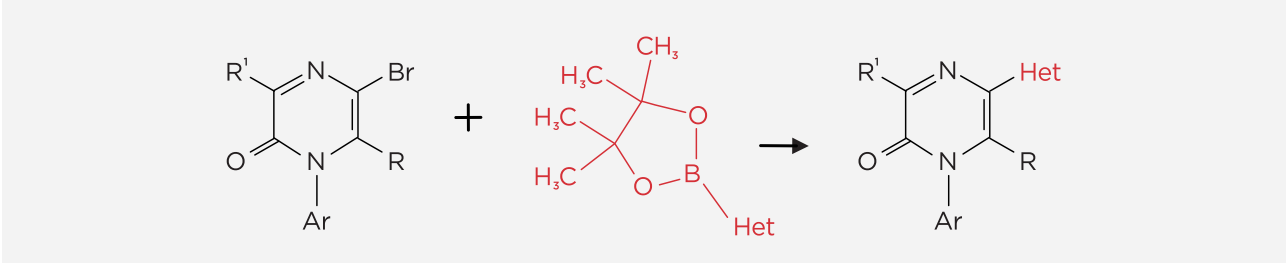
# Case Study: Solvent Selection for a Suzuki Reaction

This Suzuki reaction was developed as the final synthetic step to deliver an Active Pharmaceutical Ingredient (API). The reaction proved problematic at scale with a significant reduction in yield to < 45% during the delivery of 25 kg of API for clinical development. The reaction used 5 mole%, a high loading of the air stable and reactive palladium (II) catalysts, 1,1 -Bis(di-tert-butylphosphino)ferrocene]dichloropalladium.




During the development process, decomposition of the boronic acid was observed in slower reactions, therefore, a high catalyst loading was maintained to minimise decomposition of the expensive intermediates.

## Objective: To develop a robust scalable manufacturing process for the API.

Analysis of a reaction profile and the impurities formed highlighted the rapid decomposition of both starting materials. The analysis showed that both materials were unstable under the reaction conditions with a half-life of less than 3hrs. Therefore, a study of the stability of the starting materials was undertaken. The boronic ester rapidly underwent protodeboronation in the presence of water with base and catalyst even in water immiscible solvents (Figure 1). The study also identified the slow dehalogenation of the HetBr under anhydrous conditions in the presence of catalyst and the rapid hydrolysis under aqueous conditions (Figure 2).

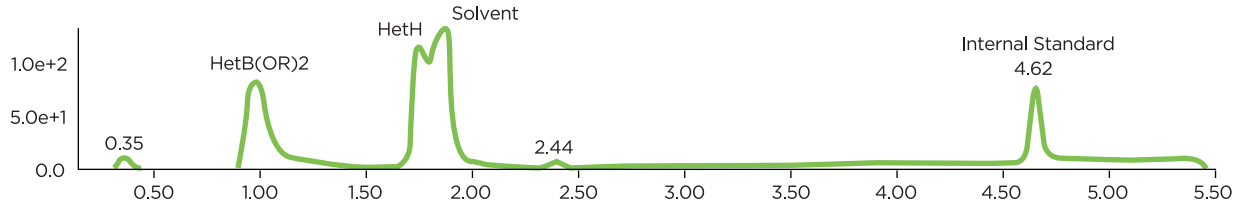



Figure 1 shows Boronic ester with water

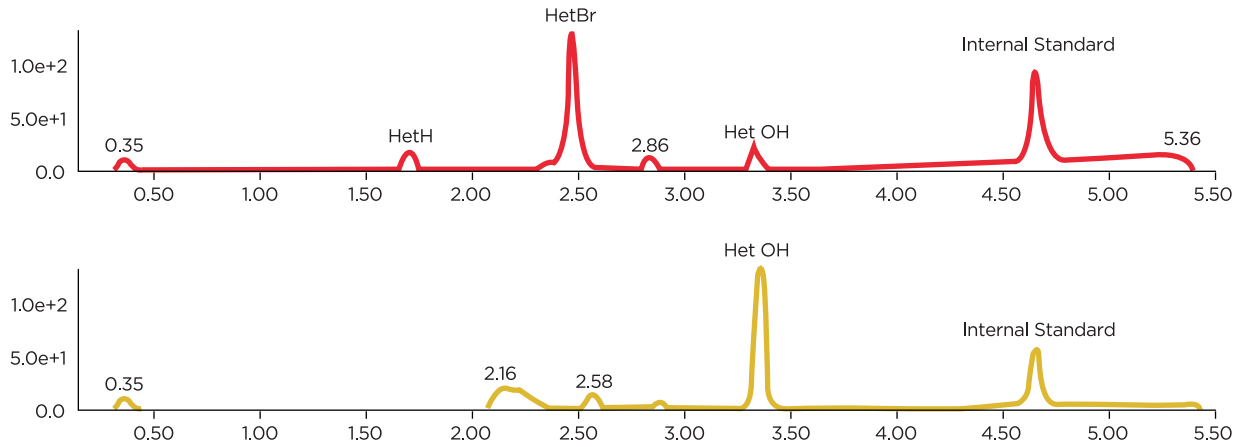



Figure 2 shows Aryl bromide under anhydrous and wet solvent conditions

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A screen of a diverse set of solvents selected using a suitable solvent principal component map was undertaken (blue dots in Figure 3). This immediately highlighted alternative solvents under which the starting materials would have a greater stability. Additional solvents were selected to aid selection of a suitable process solvent. The typical solvents for a Suzuki reaction afforded lower levels of product with significant impurities (red dots in Figure 4). While the alternative solvents (dark green dots in Figure 2) afforded very high levels of product with almost no impurities.

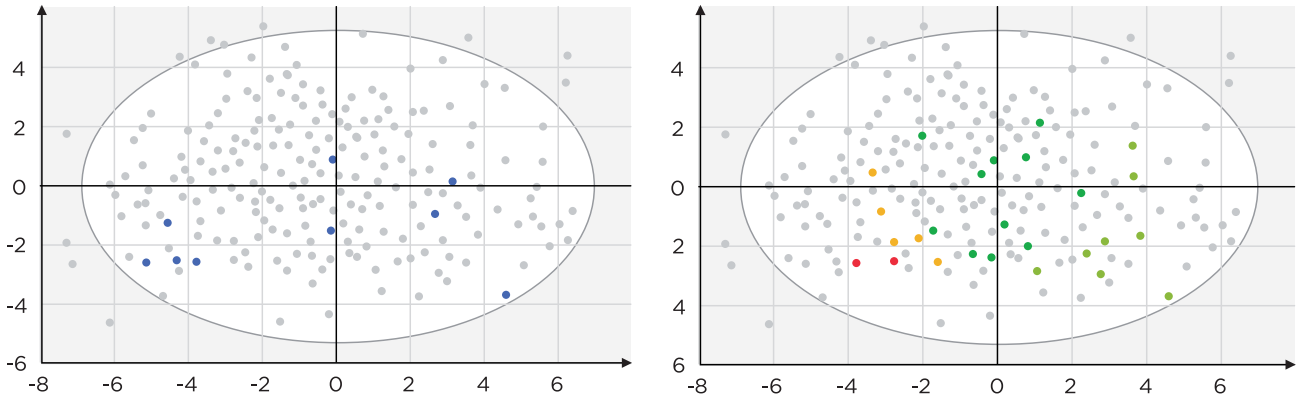


Figure 3 shows a diverse selection of solvents. Figure 4 shows results after further solvent selection.

The solvent screening identified four suitable solvents where the starting materials were stable (> 90%) for over 24hrs and under which a Suzuki reaction successfully produced the desired product in high yield. A solubility study of the product in these solvents highlighted two solvents as preferential for the isolation of the API. A final design of experiments with 8 experiments plus 3 control experiments was carried out to study both solvents along with other factors. The design lead to a robust process with higher conversion, lower impurities, 60% lower catalyst loading and a higher throughput

In summary The use of PCA to identify alternative solvents and DoE to optimise the Suzuki reaction produced a robust process which was successfully scaled up to deliver 60 kg of API. The new robust process enabled a reduction in the catalyst charge while simultaneously more than doubling the yield. This had a significant cost benefit to the project with savings of more than £140,000.



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