WHITEPAPER

De-Risking Suzuki Development Through Integrated HTE and DoE

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Executive Summary

This whitepaper demonstrates how CatSci's integrated HTE and DoE workflow, **CHETAH**, rapidly de-risked and scaled a challenging Suzuki–Miyaura coupling while maintaining impurity control and reducing catalyst loading.

- **Rapid Catalyst Identification**: High-throughput screening across three 24-well plates quickly identified XantPhos/Pd(MeCN)$_2$Cl$_2$ as the most selective and scalable catalyst system for this challenging multifunctional substrate.
- **Early Impurity Control:** Systematic screening minimised bis-addition impurity to <2 LCAP, establishing chemoselectivity early and reducing downstream purification risk.
- **Statistically Robust Optimisation:** A custom 30-run Design of Experiments (DoE) delivered a predictive model ($R^2 \geq 0.80$) enabling confident parameter selection and controlled catalyst loading reduction.
- **Cost-Conscious Development:** Catalyst loading was reduced to 2 mol% while maintaining performance, balancing process efficiency with commercial viability.
- **Seamless Translation to Scale:** Conditions progressed smoothly from automated miniaturised screening to 250 mg and 25 g jacketed reactor scale with consistent impurity profiles.
- **Faster Decisions:** CHETAH reduced optimisation timelines and material usage while delivering a scalable, development-ready Suzuki coupling process.

Developmental Impact

- **3 screening plates**
- **30-run predictive DoE**
- **Catalyst reduced to 2 mol%**
- **<2 LCAP impurity control**
- **Translation to 25 g scale**

The Team

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1. Introduction: Challenge

Scaling a promising reaction from milligram discovery chemistry to a robust, manufacturing-ready process is often far from straightforward. Conditions that perform well in early development often fail to deliver the selectivity, yield, and/or robustness required for scale, leaving process teams facing long optimisation cycles and significant resource demands. High-throughput experimentation (HTE) offers a powerful alternative, enabling rapid, data-rich exploration of reaction parameters to identify scalable conditions far earlier in development. By systematically screening catalysts, ligands, solvents, bases, and temperatures in parallel, HTE transforms reaction optimisation from a sequential trial-and-error exercise into a strategic, data-driven process that accelerates the path to scalable, reliable chemistry.

At CatSci, our High-Throughput Experimentation platform combines rapid proof-of-concept screening with advanced, data-driven optimisation workflows called **CHETAH** (see article here). Early PoC screens enable fast identification of viable reaction pathways, and reaction optimisation is accelerated using Design of Experiments (DoE), Bayesian optimisation, and/or AI-guided approaches. This integrated approach aligns with the milestones of our customer projects, from route scouting to process development, allowing us to efficiently explore chemical space and generate robust datasets that support the development of scalable, reliable processes.

In this white paper, we demonstrate our workflow through the optimisation of a Suzuki–Miyaura coupling, highlighting how our high-throughput platform accelerates the transition from early reaction screening to robust, scalable process conditions.

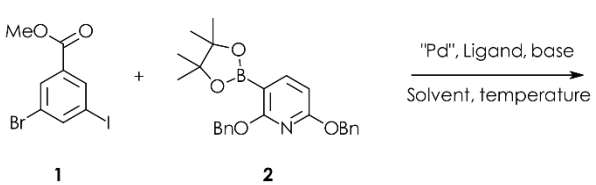
2. High-Throughput Screening Strategy

2.1. Reaction Overview

For this optimisation, we selected a model transformation inspired by challenges frequently encountered in customer projects. We chose methyl 3-bromo-5-iodobenzoate **1** as the substrate, reflecting the types of multifunctional compounds that often complicate development work. Molecules containing multiple reactive sites introduce competing pathways, making control of regioselectivity, bis-addition, and dehalogenation critical to achieving the purity and robustness required for scale-up. Boronic ester partner **2** was selected for similar reasons; this family of boronic esters is widely used as precursors to glutarimide motifs, but present well-known challenges in cross-coupling chemistry, including deborylation, homo-coupling, and stalled reactions.

Our optimisation targets were aligned to those of a typical customer project: achieve >90 LCAP for product **3,** limit bisaddtion product **4** to <2 LCAP, and identify reaction conditions suitable for scale-up. A common constraint in reaction development is the limited availability of starting materials, whether supplied by the customer or generated in-house during route scouting. Miniaturised high-throughput screening (HTS) allows us to maximise the value of scarce material while rapidly exploring a much broader range of conditions.

To execute this campaign, we leveraged CatSci's recently upgraded HTE platform, including the Labman MultiDose for automated solid dispensing, the Hudson Scorpion™ for chemistry for precise, low-volume liquid handling, and tumble stirrer and reactors from V&P Scientific. Operating the liquid and solid handling systems within a large inert-atmosphere glovebox enables reliable miniaturisation while eliminating false negatives caused by catalyst deactivation from air or moisture, which is an important consideration when screening at lower volumes. This level of control is particularly important for high-throughput



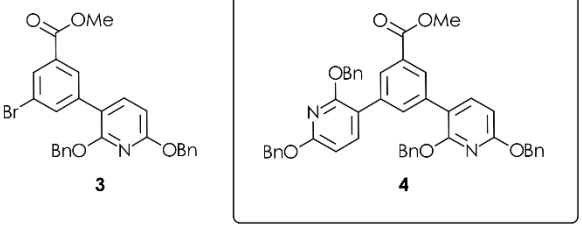
Scheme 1: Suzuki–Miyaura coupling for optimisation.

Figure 1: CatSci HTE Equipment Suite

chemistry applications, where consistency in solid dosing and liquid handling directly impacts data quality and reproducibility across screening plates.

2.1. Initial Screening

For the first screening plate, we limited the catalyst set to a small number of well-established Suzuki–Miyaura palladium precatalysts. Using precatalysts helps avoid potential activation issues and keeps the screen agnostic to the



specific Pd source, which can be explored at a later stage. We selected toluene/water and 1,4-dioxane/water as solvent systems, allowing us to compare biphasic versus homogeneous reaction environments. The primary objective of this first plate was to map ligand performance and identify the Pd/ligand combinations most likely to deliver the desired chemoselectivity. Once the initial trends are established, the ligand library can be expanded in a more targeted and data-driven manner, accelerating progression toward scalable reaction conditions.

For the base, we chose K_3PO_4 and Et_3N, two broadly effective options that activate most precatalysts and provide an early comparison between inorganic and organic bases. Reactions were run at elevated temperature (70 °C) to ensure full catalyst activation (J. Am. Chem. Soc. 2021, 143, 25, 9682–9693). The first screen used a 24 well plate on a 50 mg scale with 5 mol% Pd loading. Execution of these multi-parameter screening plates relies on consistent and precise liquid handling, ensuring that variations in reaction outcome reflect true chemical effects rather than experimental variability. Our key readouts were overall conversion (as measured by product LCAP) and the LCAP of bisaddition product.

We typically visualise screening results using complementary heatmap and pie chart formats. The heatmap provides a rapid overview of reaction performance across the plate, quickly highlighting conditions that deliver the highest conversion. In parallel, pie charts offer a more detailed view of product distribution. This is particularly valuable in this case, where controlling formation of the bis-addition impurity is a critical metric for assessing reaction selectivity and scalability.

From the heatmap a clear trend emerged, as bidentate ligands outperformed monophosphine ligands across the screen. $Pd(dppf)Cl_2$ showed higher performance in dioxane/water, whereas XantPhos Pd G4 performed better in toluene/water. Meanwhile, the pie chart analysis allowed us to visualise the selectivity profile of each catalyst system. Both $Pd(dppf)Cl_2$ and XantPhos Pd G4 afforded notably lower levels of bisaddition product, making them strong candidates for further optimisation. Most other catalysts showed poor chemoselectivity, with high levels of bisaddition. We observed little difference between NEt_3 and K_2CO_3, however, NEt_3 was preferred for future work to maintain

a homogeneous reaction mixture and avoid mixing challenges.

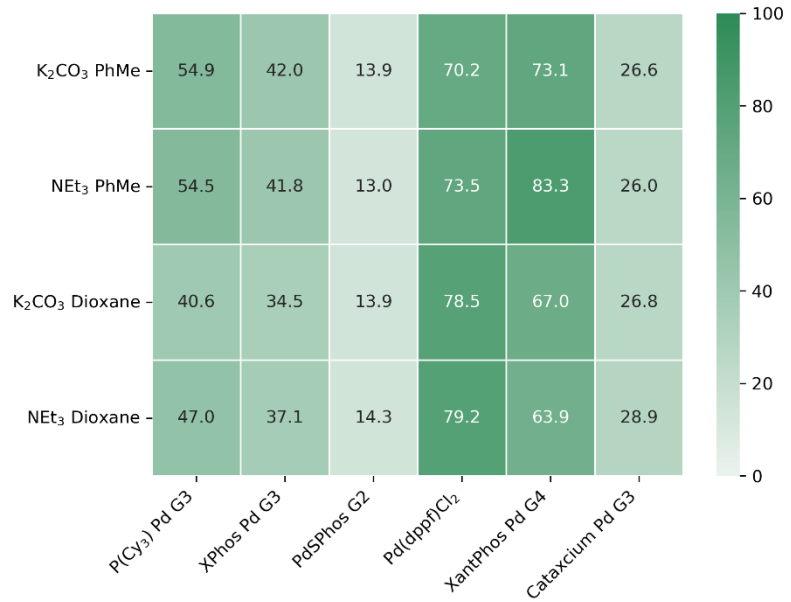


Figure 2: Heatmap of product LCAP for the first screening plate

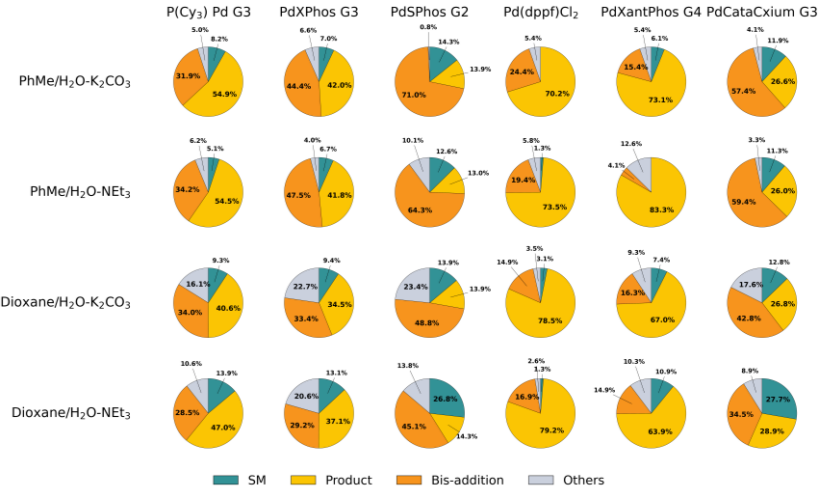


Figure 3: Pie charts visualisation of the first screening plate

The next stage of the investigation focused on evaluating alternative palladium precursors while expanding the ligand set around the initial hits. To ensure direct comparability with the primary screen, the core reaction conditions were maintained: a toluene/water solvent system, NEt_3 as the base, and a catalyst loading of 5 mol%. Maintaining these parameters allowed us to assess the impact of ligand structure and palladium source on catalytic reactivity and selectivity.

We selected a series of bidentate ligands with steric and electronic profiles similar to, but distinct from, dppf and XantPhos. Bite angle was used as a key design parameter, considering dtbpf vs. dppf (104.2° and 99.0°), and DPEPhos vs. XantPhos (104° and 108°). Larger bite angles are generally associated with enhanced efficiency in Pd-catalysed cross-couplings. However, in this system, we anticipated a competing effect: wider bite angles may also facilitate bisaddition pathways, increasing the formation of undesired product **4**. Electronic effects were also considered. Replacing aryl substituents with alkyl groups increases the electron density at the phosphorus atom, facilitating oxidative addition, a key step in activating the aryl halide (Acc. Chem. Res. 2008, 41, 11, 1461–1473). Conversely, increasing the steric bulk of the substituents can favour reductive elimination, potentially improving efficiency but also influencing the ratio between mono and bisaddition towards the unwanted impurity.

Heatmap analysis of the second screening plate clearly indicated that dtbpf is not a viable ligand for this transformation, showing consistently low conversion across

all Pd sources. In contrast, dppf, XantPhos, and DPEPhos each afforded promising conversion, reinforcing the trend observed in the first plate that bidentate ligands with appropriate steric and electronic balance are required for this substrate. Notable differences between the palladium precursors were also observed. $Pd_2(dba)_3$ was generally less efficient than the alternative sources screened, although it performed comparatively better when paired with DPEPhos. These results highlight the importance of jointly optimising both ligand and palladium source during high-throughput screening.

Turning to the pie chart visualisation, a more complete picture of the reaction outcomes emerged. Although several conditions delivered high product LCAP values, many of these were accompanied by correspondingly elevated levels of bis-addition impurity 4. In contrast, two catalyst systems stood out for displaying good conversion with notably lower bisaddition levels: XantPhos/$Pd(MeCN)_2Cl_2$ and $Pd_2(dba)_3$/DPEPhos, which produced only 6.9 and 4.6 LCAP of 4 respectively (with DIPEA as base). These results align well with the trends observed in the heatmap and highlight these two systems as the most promising candidates for further optimisation.

The pie chart analysis also reinforces the conclusion that dtbpf is unsuitable for this transformation, with the low apparent conversion largely attributable to substantial formation of the bis-addition product **4**. This supports our earlier hypothesis that larger bite angles and bulkier ligand frameworks can exacerbate bisaddition, making them detrimental to our goal of minimising impurity **4**.

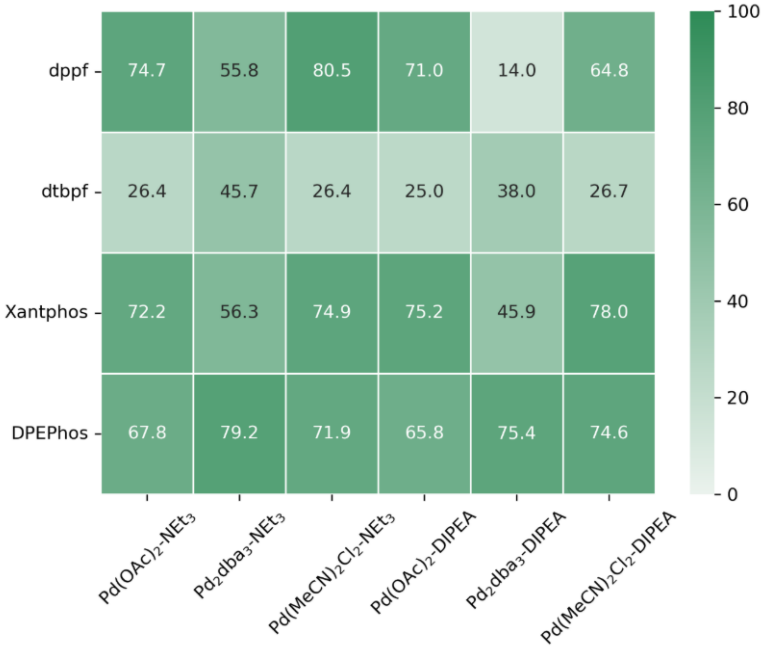


Figure 2: Heatmap of product LCAP for the second screening plate

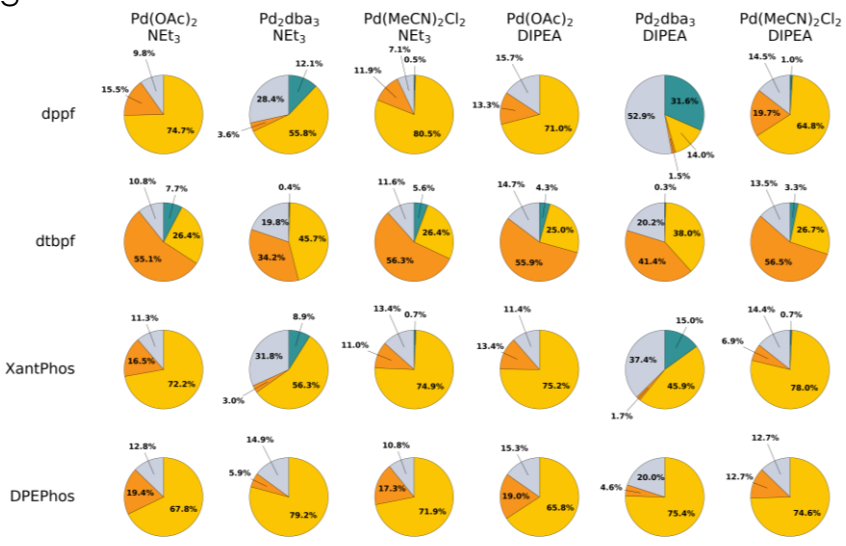


Figure 3: Pie charts visualisation of the second screening plate

To differentiate between the two most promising catalyst systems, XantPhos/$Pd(MeCN)_2Cl_2$ and $Pd_2(dba)_3$/DPEPhos, a final 24 well screening plate was conducted, focusing specifically on the influence of solvent and water content. Reaction parameters were maintained in line with the previous screening campaigns to isolate solvent effects and enable a direct comparison of catalyst system performance. The best performing combinations were XantPhos/ $Pd(MeCN)_2Cl_2$ in isopropyl acetate (iPrOAc)/water and toluene/water, and DPEPhos/$Pd_2(dba)_3$ in CPME/water. Although toluene and CPME showed promise, they are Class 2 solvents under ICH guidelines, and therefore minimising or avoiding them is preferable. In addition, the use of $Pd_2(dba)_3$ was deprioritised due to the known batch-to-batch variability, which can result in inconsistent catalytic activity (Organometallics 2012, 31, 6, 2302–2309). This poses a risk when scaling up, as it would require additional control over supplier specifications / quality assessment for each batch, which is not ideal for a robust commercial process.

Examining the pie chart visualisation provides deeper insight into the influence of water and solvent on each catalytic system. For XantPhos/$Pd(MeCN)_2Cl_2$, a lower amount of water in biphasic systems resulted in a decrease in conversion to product **3**, but also a substantial reduction in impurity **4**, with some starting material **1** still present. This profile is encouraging for optimisation, as there is scope to further increase conversion while maintaining control over bisaddition. A comparable reduction in the bis-addition impurity **4** formation was observed with the $Pd_2(dba)_3$/DPEPhos catalyst system. However, in this case little to no starting material remained, suggesting that the reaction was already approaching maximal conversion and leaving less flexibility to further tune the reaction conditions without risking increased impurity formation. This trend was consistent across toluene, MeTHF, CPME, and iPrOAc.

In contrast, the homogeneous reaction systems, MeCN/water and IPA/water, showed increased formation of the bis-addition impurity. In IPA/water, with lower water content, conversion to product **3** increased but this was accompanied by higher levels of impurity **4**, while in MeCN/water total impurity level rose, including impurity **4**. These observations reinforced the conclusion that biphasic systems provide a more favourable balance between conversion and selectivity for this substrate.

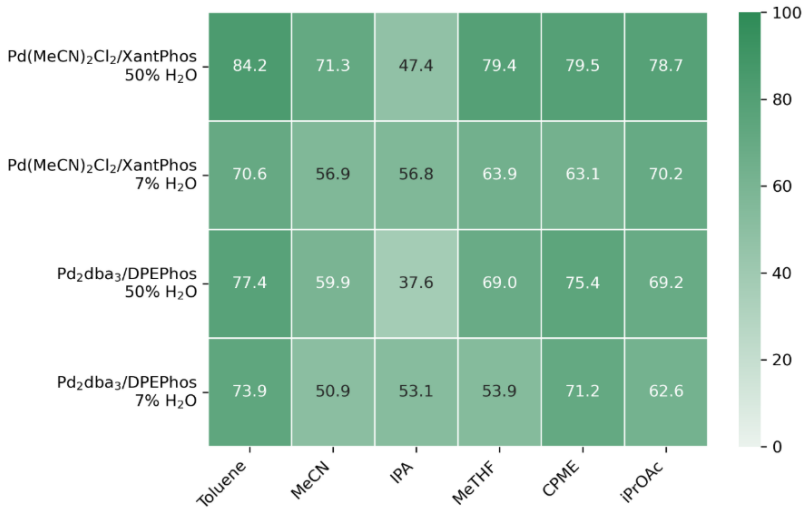


Figure 4: Heatmap of product LCAP for the third screening plate

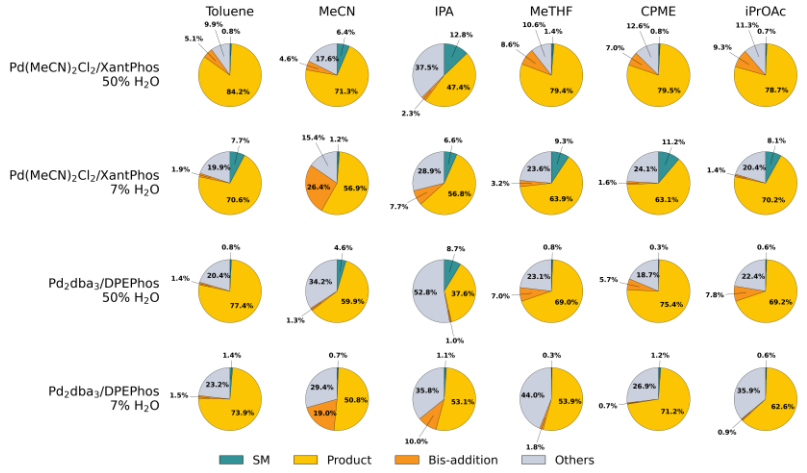


Figure 5: Pie charts visualisation of the third screening plate

Across the three screening plates, a clear picture of the optimal catalytic environment emerged. The combination of XantPhos and $Pd(MeCN)_2Cl_2$ consistently delivered the most favourable balance of conversion and chemoselectivity, particularly in iPrOAc with lower levels of water present. Under these conditions, formation of the bis-addition impurity was effectively minimised, with residual starting material present. This outcome is advantageous from a process optimisation perspective, as it leaves scope to further increase conversion without compromising selectivity. In contrast, across all the screens, alternative ligand–Pd combinations exhibited higher impurity levels, limited room for optimisation, and/or or practical concerns such as solvent classification and catalyst reproducibility.

With a robust catalyst–solvent system identified, the next step was to refine the reaction parameters in a systematic manner. A Design of Experiments (DoE) study was therefore undertaken to map the key variables influencing conversion and impurity formation, with the objective of defining a scalable process.

3. DoE for Reaction Optimisation

3.1. DoE Setup

For the optimisation phase, a DoE approach was favoured over a Bayesian optimisation, to provide a better understanding of the reaction and obtain a predictive model. A custom design was selected, as standard screening designs such as Definitive Screening Designs (DSD) do not provide enough datapoints to build a reliable predictive model (particularly when curvature and interactions are expected) but on

the other hand, a full factorial design would have required substantially more experimental runs. The custom design allowed us to include the necessary quadratic and interaction terms while minimising the total number of reactions, resulting in a statistically efficient and experimentally

practical design.

Key process variables were selected based on their expected impact on reaction performance: water content, equivalents of boronic ester, base equivalents, reaction temperature, reaction concentration (RV), and catalyst loading. The ability to execute these multi-factor experimental designs in a reliable and reproducible manner is enabled by automated liquid handling, which ensures accurate dosing of reagents across all experimental conditions. The responses targeted maximisation of product yield and minimisation of the bis-addition impurity.

The initial DoE employed the system identified during previous screening (iPrOAc, XantPhos/Pd(MeCN)$_2$Cl$_2$, DIPEA), but high variability was observed. This was attributed to inconsistent in situ activation of the Pd/ligand system. To improve reproducibility, we reverted back to the precatalyst, Pd(XantPhos)Cl2, for the DoE optimisation. In total, 30 reactions were performed to build the predictive model. The initial design comprised 24 runs, including four centre points to assess curvature and experimental variability. A further six experiments were added in a second iteration to augment the design and improve model robustness.

Factors (evaluated at 3 levels)	Value	
	Low (-)	High (+)
Water in iPrOAc % (v/v)	30	50
ArBPin eq.	1.0	1.5
DIPEA eq.	1	3
Concentration (solvent RV)	8	20
Temperature	50	80
mol% of Pd	1	5
Custom design		
Component	Numbers of runs	Purpose
Main DoE	20	Estimate main effects and interactions
Centre points	4	Detect curvature and assess variability
Augmentation runs	6	Improve model prediction and fill design space
Total	30	Final predictive model

Table 1: Custom DoE summary

3.2. Model Outputs and Interpretation

Using data from the 30 reactions, a predictive model was fitted using standard least squares regression. The main factors were identified and ranked by LogWorth (see Pareto chart), where values above 2.0 indicate highly significant effects. The most influential variable was the amount of DIPEA, followed by reaction temperature. In contrast, reaction concentration showed little significance. Second-order effects were also observed, including interactions between base loading and catalyst loading, as well as curvature in the effect of water content.

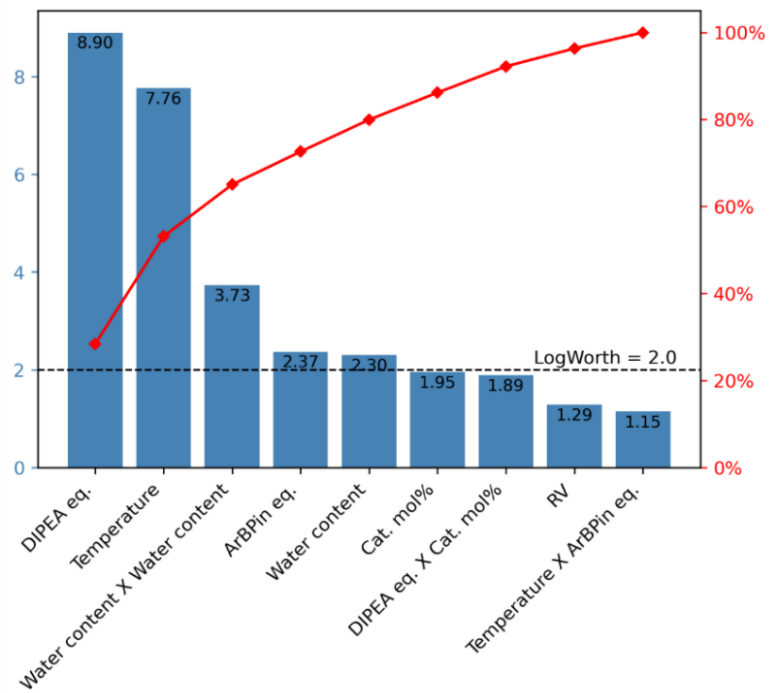
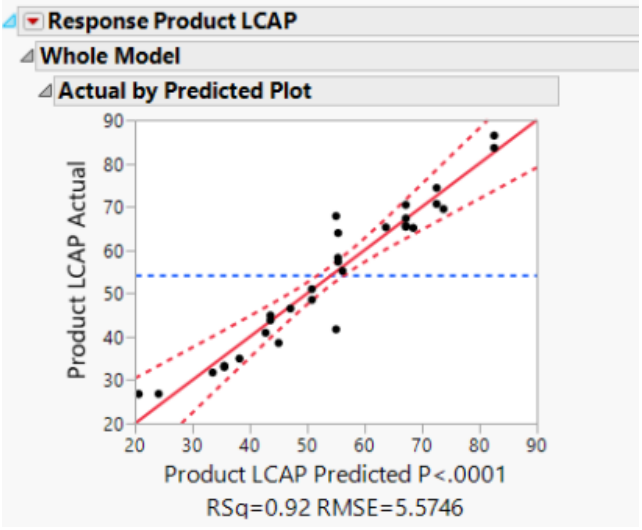
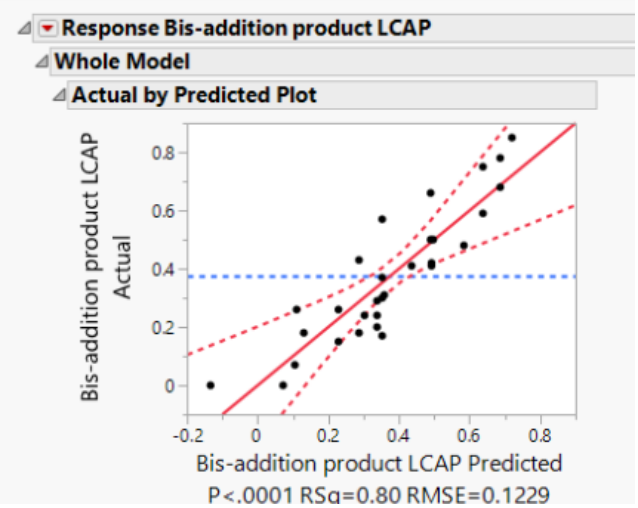


Figure 6: Pareto chart of factors and secondary interactions from the DoE study

A model incorporating the significant variables provided strong predictive performance for product yield and reasonable prediction of the bis-addition impurity levels. The latter was typically observed at very low levels (<2 LCAP), which limited variability in the dataset and consequently reduced model predictivity. Model quality was assessed by comparing predicted and observed values using R^2 and adjusted R^2, where values closer to 1 indicate a better fit. The adjusted R^2 also penalises unnecessary terms, helping identify model over-parameterisation.

For both responses, R2 values were 0.80 or higher, indicating a good predictive model. The bis-addition impurity gave the lower R2, with an adjusted R^2 of 0.71 (R^2 = 0.80), suggesting the model captures the general trend but could be improved with additional design points. While further augmentation of the design could refine the response surface, the current model was considered sufficient to support initial scale-up and de-risk the process prior to a demonstration batch. Model validity was further supported by lack-of-fit tests, where p-values >0.05 confirmed that the observed effects arise from true factor relationships rather than random variation.





	Product LCAP	Bis-addition LCAP
R-squared	0.92	0.80
Adjusted R-squared	0.89	0.71
Lack of Fit (Prob>F)	0.801	0.515

Table 2: Summary of statistical values from DoE study

3.3. Final Condition Selection

After confirming model validity, JMP® Prediction Profiler was used to maximise overall desirability across the responses. Catalyst loading was then manually reduced to account for cost considerations while maintaining acceptable predicted performance. This identified the following optimal conditions: 41% water (v/v), 1.0 equiv. boronic ester, 80 °C, 2 mol% catalyst, and 3 equiv. DIPEA. Reaction concentration showed minimal influence and was set to 8 RV (lowest end of tested range) to minimise solvent usage and cost. Use of the Prediction Profiler tool also highlighted the curvature observed in the water content, indicating a non-linear relationship with reaction outcome and highlighting the importance of maintaining water content within the optimal range.

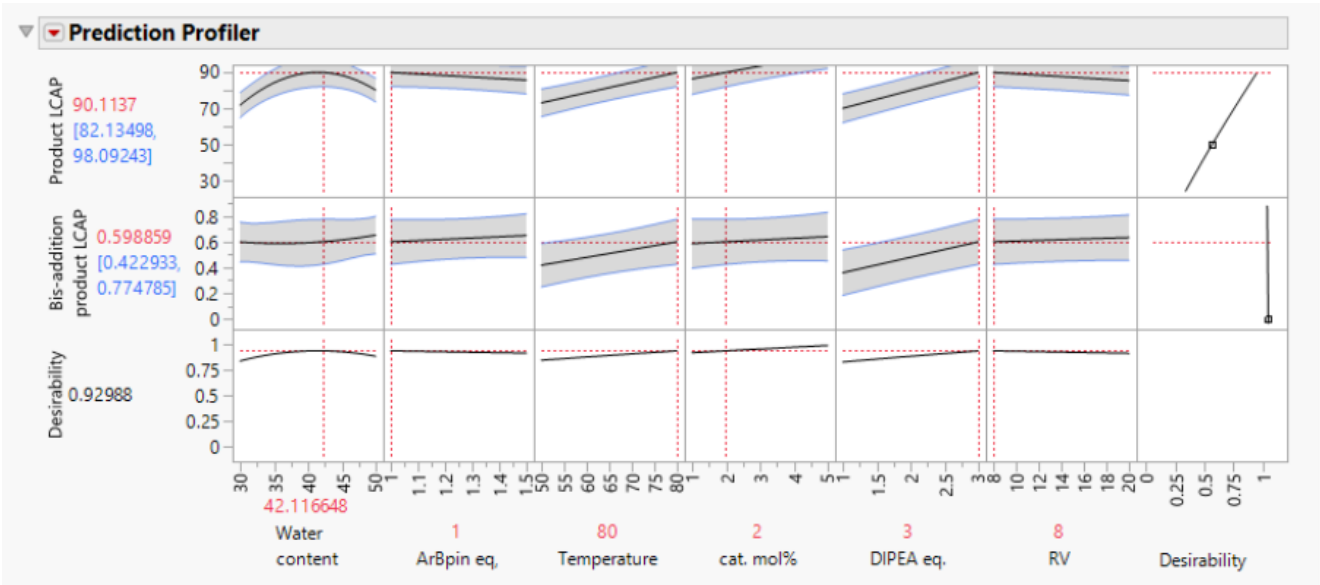


Figure 7: JMP® Prediction Profiler for DoE optimisation

4. Scale Up of Optimum Conditions

4.1. Initial Testing Outside Glovebox

After identifying optimal conditions from the DoE study, the reaction was evaluated under conditions more representative of a process environment, i.e. outside the glovebox. To better mimic scale-up operation, the protocol was modified, particularly the sparging strategy and order of addition. The revised approach was first tested on 250 mg scale; the aryl iodide substrate and the boronic ester were dissolved in iPrOAc/water, followed by the addition of DIPEA. The reaction mixture was then subsurface sparged with nitrogen for 20 minutes, then Pd(XantPhos)Cl_2, was added and sparging continued for an additional 5 minutes. The reaction was then heated to 76 °C (internal temperature) and maintained for 24 hours. Comparison of the LCAP data showed good agreement with the values predicted by the DoE model, with 0.5 LCAP bis-addition impurity, although product LCAP was slightly lower than predicted at 85.9 LCAP (predicted 90 LCAP from DoE).

Experiment	ArBpin eq.	Cat. Loading (mol%)	iPrOAc/ Water (v/v)	DIPEA eq.	Solvent RV	Temp. (°C)	Product LCAP	SM LCAP	Bis-addition LCAP
DoE Predicted	1	2	3/2	3	8	80	***90***	-	***0.60***
250 mg Scale Test	1	2	3/2	3	8	76	85.9	2.6	0.5

Table 3: DoE validation with scale-up protocol

4.2. Scale up to Jacketed Reactor

The reaction was then scaled to 25 g in a 500 mL jacketed reactor equipped with an overhead stirrer and pitched-blade impeller. The time course profile showed steady product formation with consistently low levels of the bisaddition impurity. After 24 hours, conversion had begun to plateau, and a kicker charge of 1 mol% catalyst was added at the 28 h mark. Stirring for an additional 20 hours resulted in improved conversion while maintaining a clean impurity profile.

The bis-addition impurity remained <2 LCAP, consistent with small-scale results, and the final composition closely matched earlier experiments. The 1 mol% catalyst kicker charge added after 28 h did not significantly increase the reaction rate; this suggests the limitation may arise from substrate availability rather than catalyst activity. Further kinetic studies would be required to confirm the cause of the rate decrease.

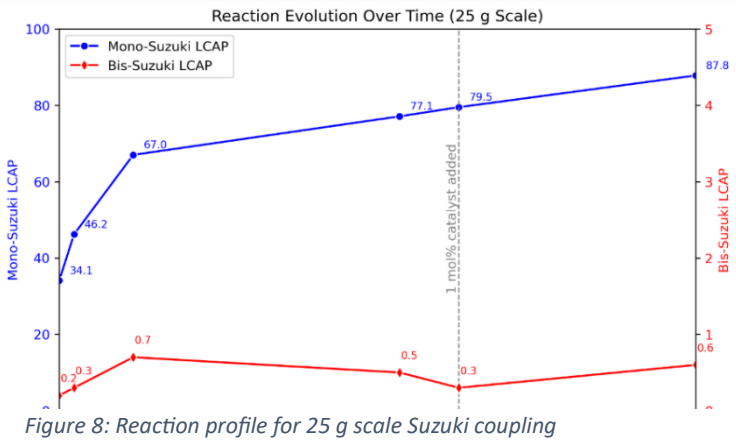


Figure 8: Reaction profile for 25 g scale Suzuki coupling

Comparison of the scale-up reaction, DoE validation runs, and model predictions highlights the value of the HTE-driven development approach. All three data sets show consistent LCAP trends, with the larger scale reaction simply requiring more time to reach its endpoint, which is an expected effect of increased reaction volume. Importantly, the conditions translated smoothly from automated small-scale screening to a 500 mL jacketed reactor, demonstrating good scalability.

While product LCAP at 25 g was slightly below the modelled 90 target, this likely reflects scale-dependent factors such as heat transfer, mixing, and sparging efficiency, which require further optimisation. Encouragingly, the impurity profile closely matched DoE predictions and remained <2 LCAP, supporting downstream impurity control and overall process robustness.

Experiment	ArBpin eq.	Cat. Loading (mol%)	IPrOAc/ Water (v/v)	DIPEA eq.	Solvent RV	Temp. (°C)	Product LCAP	SM LCAP	Bis-addition LCAP
DoE Predicted	1	2	3/2	3	8	80	90	-	0.6
250 mg Scale Test	1	2	3/2	3	8	76	85.9	2.6	0.5
25 g Scale	1	2+1	3/2	3	8	76	87.8	2.3	0.6

Table 4: DoE validation with scale-up protocol

5. Workflow Impact and Lessons Learned

This case study demonstrates how the CatSci HTE platform enables rapid, data-driven development of challenging transformations, exemplified here with a Suzuki–Miyaura coupling. Early screening rapidly identified a catalyst system that gave high regioselectivity and minimised formation of the bis-addition impurity. A focused DoE study then refined the reaction parameters to deliver robust conditions suitable for scale-up, which were subsequently validated in a reactor under process-relevant operating conditions.

By combining automation, parallelisation, and miniaturisation, our HTE workflow enabled broad exploration of reaction space using notably less material and time then would be required for traditional screening approaches. For our customers, this reaction could also be further tuned depending on the specific performance, cost, or sustainability objectives, with the same material- and time-efficient approach. Also, this methodology can be extended beyond reaction optimisation to accelerate work-up and isolation development, enabling rapid evaluation of options that might otherwise be constrained by time or resources and ultimately supporting faster, more efficient process delivery.

About CatSci

CatSci is a UK-based strategic outsourcing partner supporting pharmaceutical and biotech companies developing novel small molecule therapies and complex synthetic modalities. From route design and scale-up to analytical control and technology transfer, our integrated services help our partners deliver life changing medicines to patients faster. Our integrated capabilities span synthetic chemistry, high-throughput experimentation, catalysis, oligonucleotides, peptides, analytical science, and scale-up, delivered from secure UK laboratories.

Through structured, data-driven workflows such as CHETAH, we combine scientific rigour with digital orchestration to accelerate development timelines. By integrating experiment design, automation, analytics, and scale-up thinking from the outset, we help teams identify robust, manufacturable chemistry and build the process understanding required for confident progression toward clinical and commercial manufacture.

To discuss how CatSci can support your development programme, contact us at **enquiries@catsci.com** or visit **catsci.com.**