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How GSK are Revolutionizing HTE

Kayleigh Mercer, Investigator, Externalisation & Technical Excellence team, Medicinal Chemistry, GSK

Increasing Efficiency in Reaction Optimization Through Miniaturization

In the mid-2010s GSK embarked on a project to increase efficiency in reaction optimization by introducing/expanding the use of high throughput experimentation (HTE) in discovery chemistry. Miniaturization to plate-based chemistry offers several advantages over classical single reaction chemistry:

Better use of expert's time with automation

Cost savings through the consumption of fewer materials (catalyst, reagents, solvents, etc.)

Higher efficiency with the investigation of multiple parameters in parallel

Faster progression of projects with more data generated in less time

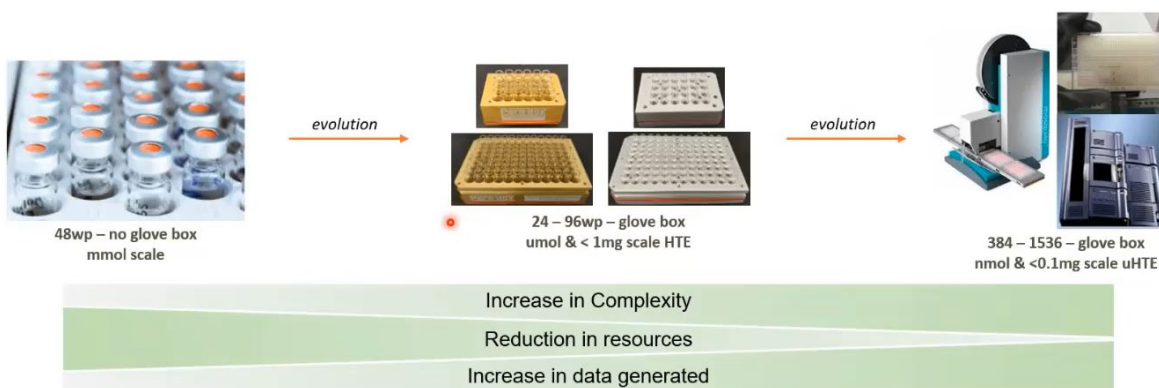


Figure 1. The evolution of GSK's HTE capabilities in medicinal chemistry from millimolar to nanomolar scale.

The recording and processing of all the data generated from HT experiments, however, is no easy task. The chemist must record experiment design, reaction parameters, chemical structures, and track sample identity from the reaction in each well through the subsequent analysis (method information, analyte information, and output analytical data).

Challenges of the Fragmented Software Environment in HTE

Historically, chemists use multiple software systems to capture HT experiments which leads to:

- Introduction of transcription errors
- Inefficiencies from moving between software systems
- Non-standardized processes that result in difficulties replicating and tracking the progress of experiments

The team at GSK identified the capture of HT experiments in their existing electronic laboratory notebook (ELN) as one of the key difficulties in reaction miniaturization.

Software for HTE—The Katalyst D2D[®] Story

Dissatisfied with the functionality of ELNs for HT experiment capture, in 2016 GSK entered a partnership with ACD/Labs to co-develop software that would support HTE workflows from experiment design to final decision-making. Goals for the first version of the software were:



Flexibility in the reagents that could be used in experiments.



High reaction fidelity—reliable and accurate capture of experiments.



Integration with chemical inventory.



Compatibility with other HTE software and hardware used.



Standardized data streams.



Ability to analyze, process, and re-process analytical data.

Katalyst D2D, introduced in 2019, delivered the HTE design and execution capabilities GSK sought.

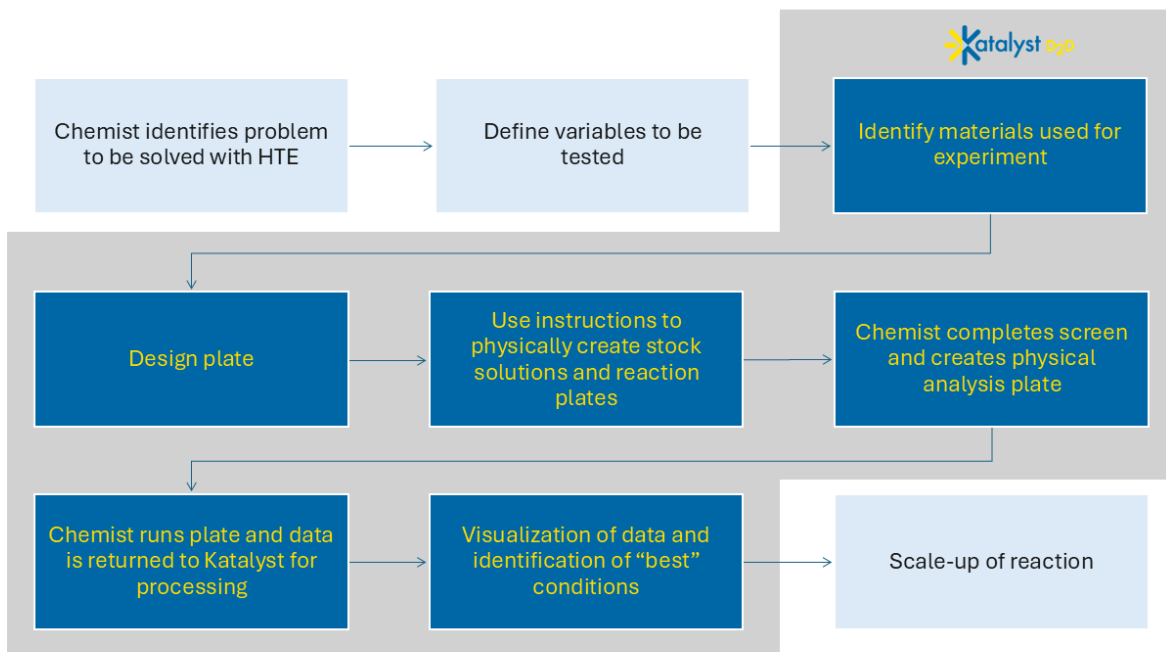


Figure 2. Katalyst D2D supports the entire HTE workflow at GSK.

Katalyst D2D In Action: Buchwald-Hartwig Coupling

The Buchwald-Hartwig coupling is a common transformation. Figure 3 represents one such reaction. There was no literature precedent for the transformation shown and while the reaction looks simple, there are potential chelation problems. From all the possible variables, the scientist wants to investigate 6 different catalysts, 2 bases, and 2 solvents.

Experiment Design Set-up

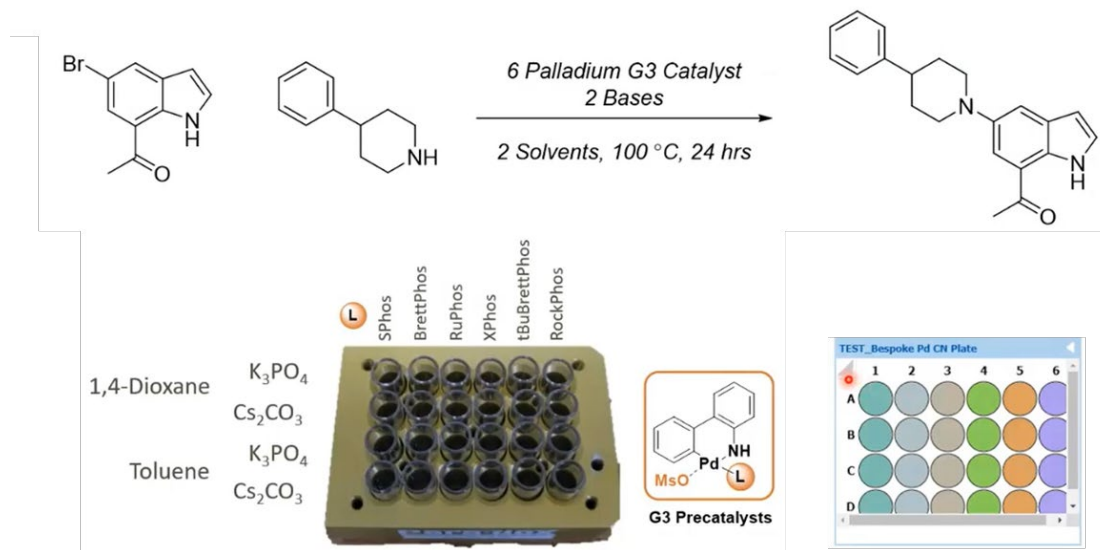


Figure 3. The chemist plans to optimize a Buchwald-Hartwig coupling with catalyst, base, and solvent as variables.

Inset bottom left: predispensed plates representing the catalyst variables (indicated by different colors) can be selected as the starting point for experiment set-up in Katalyst D2D.

Experiment variables and materials are defined in the Katalyst software.

The chemist selects from the inventory of pre-dispensed catalyst plates to get started. Analysis templates further assist the user in setting up post-reaction analysis.

The chemist drag-and-drops reagents and materials into a placeholder reaction and selects from the inventory of stock solutions (Figure 4).

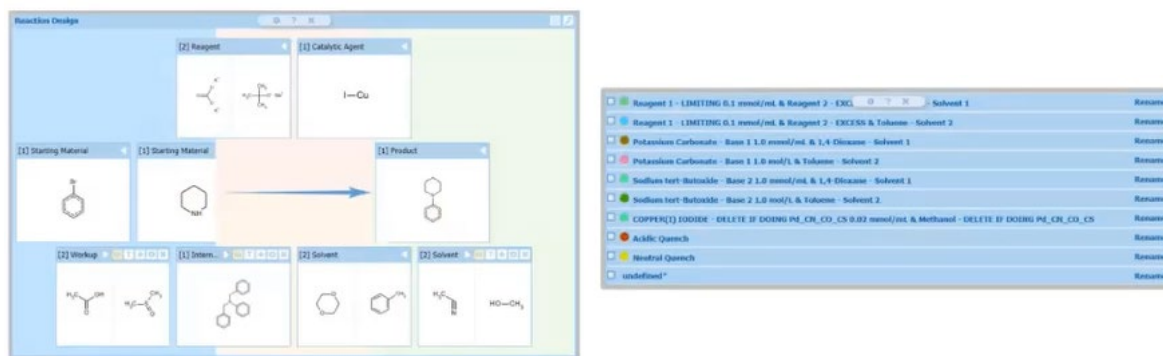


Figure 4. A placeholder reaction (left) and list of reagent stock solutions (right) help speed up HT experiment set-up in Katalyst D2D.

“Templates in Katalyst save chemists 30 minutes per experiment. It reduces the barrier for HTE uptake and expedites experiment write-up.”

The user then aspirates and dispenses stock solutions into the pre-dispensed plate which results in pie charts that represent the materials in each well (left Figure 5) and an update of the inventory. The contents of the reaction plate are dispensed into the analysis plate in the software. Clicking on an individual well pops open a window listing its contents.

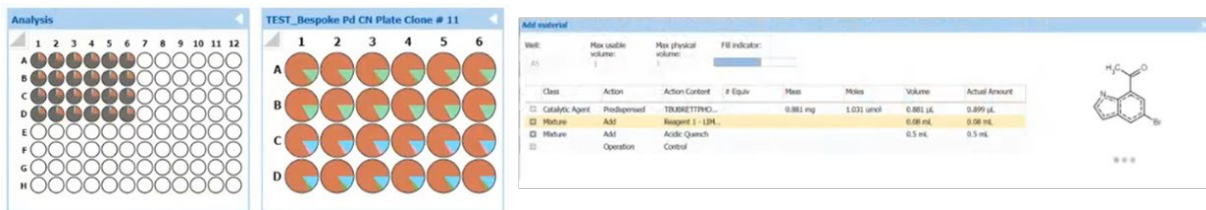


Figure 5. Katalyst D2D software: analysis plate (left), reaction plate (center), a list of contents for an individual well in the plate (right).

Katalyst accurately represents the in-laboratory workflow, delivering traceable reactions with high fidelity.

HT Experiment Execution & Analysis

The chemist then runs the plate, and analysis sequence lists are generated automatically for upload into GSK's LC/MS systems.

“Analysis sequence files in Katalyst save the user 10 mins per plate. Previously we would have to write those long input lists into an Excel file.”

Katalyst D2D sweeps analysis results from the instrument, for visualization and review. Analytical data is processed on the web and the software provides a consolidated review of the results with direct links back to each individual well. There is also an option for users to re-process data as necessary. Finally, the software enables the chemist to review their results by a variety of methods (color/size heatmaps, pie charts, graphs, scatter plots, etc.).

“Katalyst D2D gives us the flexibility to identify the best reaction conditions using the heat map and well-size visualization, or by creating charts and plots of our own.”

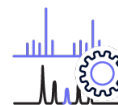
How Katalyst is Helping GSK Be Successful in HTE



Reduction of user error with a single interface for the HTE workflow.



Easy, digitalized access to materials inventory with automatic update.



Automated LC/MS data transfer and processing.



Lower barrier to HTE allowing more chemists to leverage the technology.



Easy-to-use web interface

“Katalyst lowers the barrier to HTE and enables more chemists to carry out these kinds of reactions.”

Future Directions of Katalyst D2D-Supported HTE at GSK

High Density Direct-to-Biology

The team wants to significantly accelerate hit identification by testing crude reaction mixtures without prior purification in a direct-to-biology (D2B) approach. This work is done using 1536 well-plates.

“The manual design of these high-density experiments can be complex and very tedious. We want to be able to automate aspirate/dispense patterns in Katalyst to speed up manual plating from several hours to something more manageable, with good performance.”

Leveraging Standardized HT Data to Build Predictive Models

“We want to leverage AI/ML to help design experiments and give us answers more quickly. We’re starting to pull data out of Katalyst as JSON files and push it into data visualization tools like Spotfire to understand trends and potential for data science applications. We want to further our research at high speed, ultimately to benefit patients who are in need of medicines.”

Process Chemistry Workflow Development

Fine-tuning Katalyst for parallel experimentation in process chemistry automated some of our previous manual tasks and has offered a more integrated user experience to experimental design, data capture, and data analysis. Katalyst couples this with a package of back-end experimental metadata and analytical data from each experiment that are essential to our data reuse.

Related Resource

Webinar: “[Enabling End-User HTE at GSK](#)”