Improving the Efficiency of Catalyst Screening in Drug Substance Development

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Introduction

Catalyst screening is an important part of process route scouting in pharmaceutical drug substance development. Comprehensive catalyst screening provides breakthroughs in problematic synthetic conversions and leads to processes that are more efficient.

The Challenges of Catalyst Screening

Chemistry that involves catalysts is highly specialized: catalysts are often air sensitive; reactions may be carried out under pressure, and are often conducted initially at small (μM) scale. Furthermore, synthetic target molecules in R&D are becoming more complex requiring complex synthetic routes. As a result, many organizations are investing in specialized *catalysis groups* to support screening activities.

Beyond scientific challenges, there can be a variety of logistical/administrative frustrations. Successful catalysis screening groups have employed high throughput (HT) experimentation or parallel synthesis using 96-, 384- or 1536-well microplates. The intended result is to identify conditions that:

- Maximize yield of intended reaction product
- Minimize residual starting materials
- Minimize conversion to unintended reaction products

Many organizations have invested in elaborate lab automation equipment and robotics to speed process development efforts. However, the variety of systems required to support screening workflows require repeated, often-tedious transcription from one software interface to another; this increases the risk of errors and incorrect experiment conclusions.

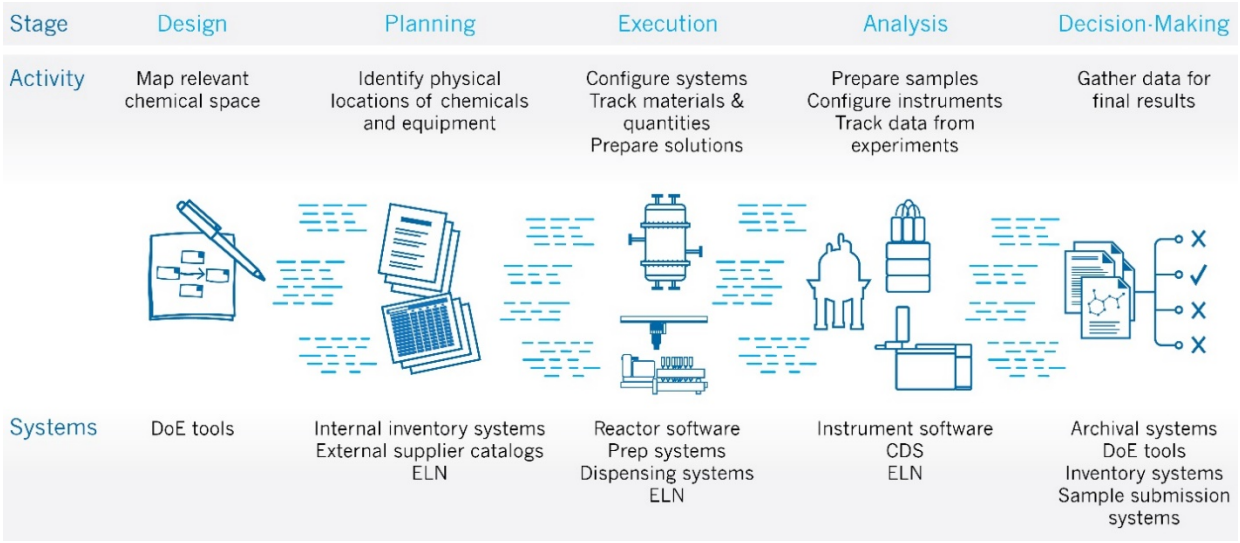


Figure 1: Typical activities undertaken and systems involved in high throughput experimentation.

Particularly, data analysis can be a significant bottleneck for HT experimentation. Optimal reaction conditions are identified by characterization of analytical experiments, typically LC and UHPLC. Unfortunately, the feasibility of batch processing relatively large (1GB per sample) LC/MS data can relegate scientists to relying on UV channel interpretation, where final quantitative results can be ambiguous.

Consequently, analytical data analysis are often performed serially (one-by-one). Even when data collection is accelerated, results must be reviewed and qualified manually; which is time consuming, laborious, prone to error, and can result in frequent reprocessing efforts. In situations where batch processing of LC/MS data is possible, the lack of connection between analytical results and individual reaction designs still requires human effort. Quantitative analysis results must also be transcribed to connect them with reaction array information. These time-consuming activities can potentially discount the overall efficiency of HT experimentation efforts.

Finally, the heterogeneity of software interfaces required throughout HT synthesis is the greatest overall challenge for decision-making. Various applications serve as data entry points and, ultimately, data sources, as outlined in Figure 1. It is extremely challenging for scientists to gather the necessary information to decide on the final result. At best, they will copy/paste information into Excel to bring it together into a single place. At worst, scientists are required to rely on their memory to assign results to the original reaction design.

Introducing Katalyst D2D—one software for HT experimentation

ACD/Labs' Katalyst D2D application has been developed to address these challenges. Katalyst is a web-based software application that supports high throughput catalyst screening—from *design* to *decide*.

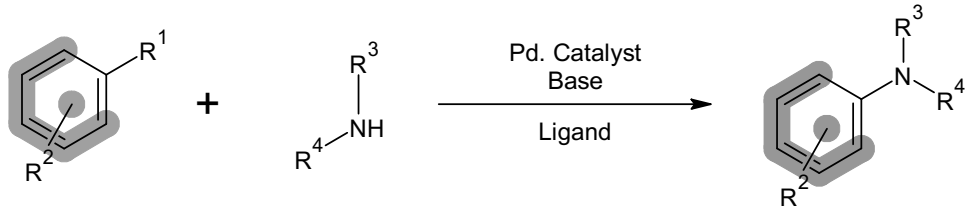
Katalyst integrates with third-party systems to provide a single interface for the design, planning, and execution of high throughput experiments. This chemically intelligent application treats the design and planning of HT experiments as a holistic scientific experiment, rather than a statistical/logistical exercise. It also eliminates the need for error-prone data transcription even for steps that require manual intervention (e.g., preparation of stock solutions).

ACD/Labs unique expertise in analytical data handling has also been built into Katalyst. HT analysis is supported with the ability to export analytical instrument-ready sample instructions from lab automation equipment to LC, UHPLC, and LC/MS instruments.

Finally, Katalyst provides easy access to analytical results in a convenient interface that connects results with the initial plate layout. This enables scientists to conveniently review and re-process data when necessary. The capability to leverage LC/MS data further supports confident decisions on the results of route optimization. Embedded plotting tools empower the scientist to conveniently review and compare experimental results in the same interface.

Catalyst Screening using Katalyst D2D

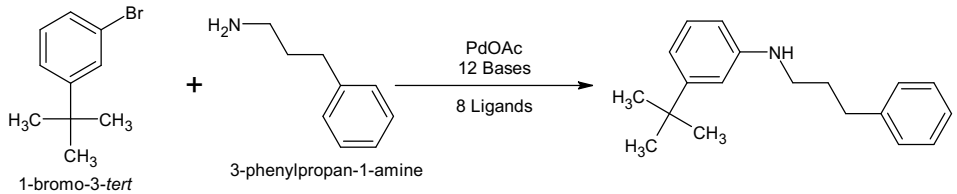
The Buchwald-Hartwig Coupling reaction (Scheme 1) is commonly employed in drug substance development. This type of reaction will be used to illustrate the benefits Katalyst affords in the high throughput workflow of catalyst screening.



Scheme 1: General scheme for a Buchwald-Hartwig reaction, where R1 = Cl, Br, OTf, R2 = non-reactive ring substituents, R3 = Alkyl, Aryl, H, and R4 = Alkyl, Aryl.

Design

The reaction outlined in Scheme 2 is to be carried out in parallel in a 96-well, 1mL plate array. The catalyst of choice is PdOAc (catalyzed couplings are often desirable in process chemistry applications). The experiment will screen a combination of 12 bases and 8 ligands. These base/ligand combinations can dramatically impact the overall specificity of catalytic activity for reactant positions of interest.



Scheme 2: High throughput experiment to screen for the best combination of bases and ligands.

Catalyst screening experiment design is entered into Katalyst by simple 'drag and drop' from an internal material query view. The interface combines materials available from in-house chemical inventory and external suppliers. Materials are placed in the appropriate position in the reaction scheme (left, right, above, or below the arrow) and their "material class" defined (starting material, ligand, base, solvent, reagent, etc.). The material table is automatically populated, eliminating the need for manual transcription of textual chemical names.

Planning

In the planning phase "96-well" plate is selected as the "array size" in the software. Pre-defined stock solutions and neat materials of reagents and catalyst are selected according to the experimental design and assigned to individual wells in the array by 'drag and drop'. Non-limiting reagents are specified by molar equivalents (as compared to the limiting reagent). The software automatically calculates appropriate volumetric and gravimetric amounts to further aid experimental planning.

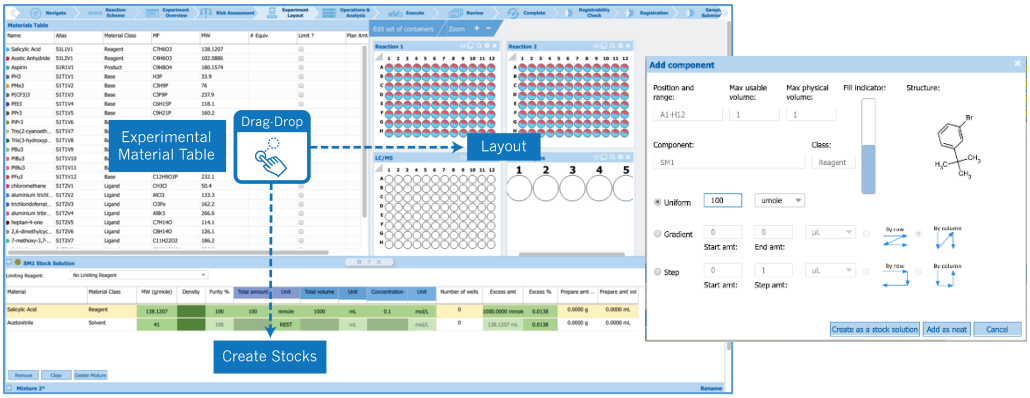


Figure 2: Visualize the dispensing of materials in the array. Chemically aware Katalyst automatically calculates material quantities according to the role of each material in the reaction scheme, and their definition in the Materials Table (stock solution or neat). The 'Fill indicator' helps ensure against over-fill. Each material is tracked throughout the experiment to assist in final analysis.

Reaction operations are defined—"simple stir" for "60 mins". Users may choose from a list of common reaction operations pre-defined in the software. Instructions for preparation of analysis samples upon reaction completion are also completed. Vessel aspiration operations are assigned from the reaction array followed by a dispense operation into analysis sample vessels. Finally, a method and correlating instruments are assigned for sample analysis. In this case, the analysis will be conducted by a Waters MassLynx LC/UV/MS system.

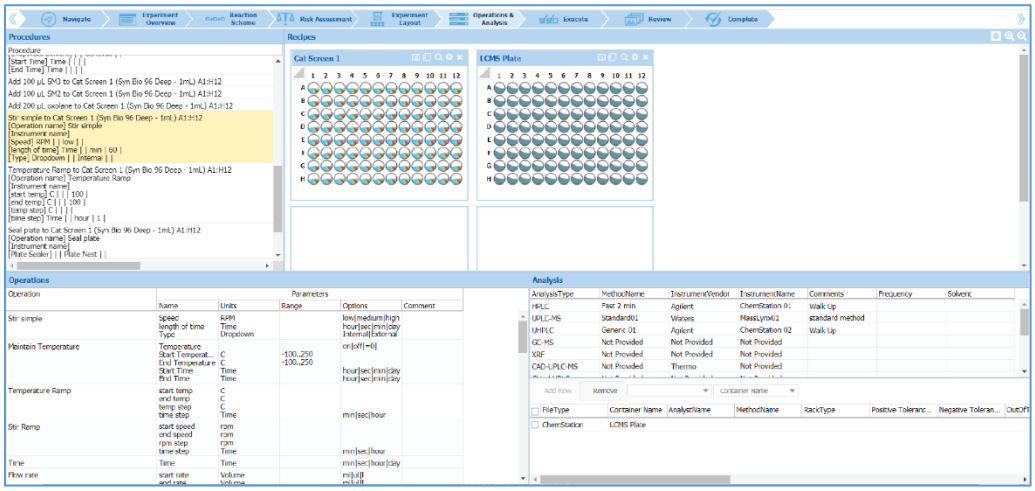


Figure 3: Apply temperature and other operations to your array. Sequence file requests can also be set up for analysis upon completion of the reaction.

Execution

Procedure lists are exported from Katalyst to lab automation equipment, dispensing equipment, and analytical instruments in machine-readable format. This eliminates the need to transcribe experiment planning information or configure instruments in their supporting software interfaces. Additionally, instruction lists are generated for steps that require manual preparation (e.g., ligand and base stock solution preparation). Integration of all necessary systems with Katalyst ensures accuracy and efficiency

in data transfer, and data integrity through tracking of each experiment in every well plate throughout the workflow. This includes connecting LC/UV/MS results back to individual well plates.

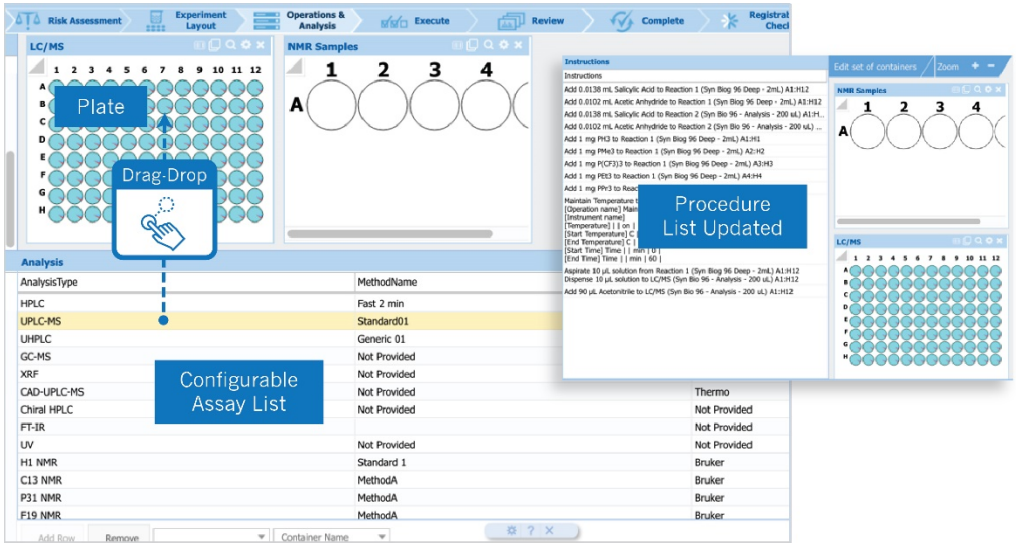


Figure 4: Procedure lists are exported in machine-readable format for robotics equipment to facilitate experiment execution and subsequent analysis. Human-readable reports may also be generated as necessary.

Analysis

Direct integration between analytical instruments and the Katalyst application allows for automation of the entire process—from design to analysis. Instructions for the sample analysis are sent to the instrument and Katalyst automatically undertakes batch processing of LC/UV/MS data once acquired. For our reaction, processing of raw data was configured to detect chromatographic components and molecular features (e.g., molecular ion, isotope distribution relative to molecular ion, observed adducts, or fragments) in the mass spectrum, followed by peak detection and integration for the UV channel. The Review Table in Katalyst is populated with area percent values and peak area ratio for the product and starting material compared to the internal standard from the quantitative UV channel.

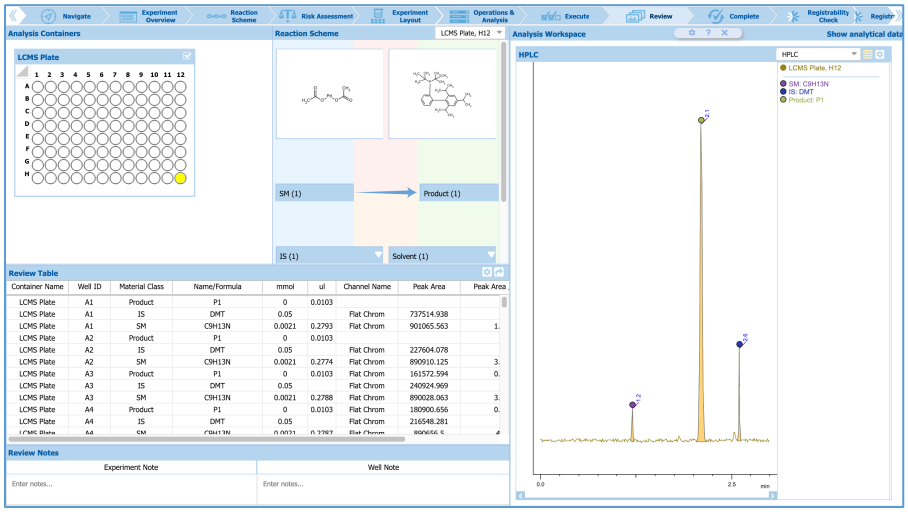


Figure 5: Results from LC/UV/MS analysis are automatically processed in Katalyst with the relevant analytical data being connected to each well in the 96-well plate array.

Decision-Making

With the connection established between each well in the array and the collected analytical results, efficient review of reaction outcomes is facilitated. Stacked chromatograms, as seen in Figure 6, enable easy comparison of the conversion of starting material to the desired product (normalized to an internal standard peak area).

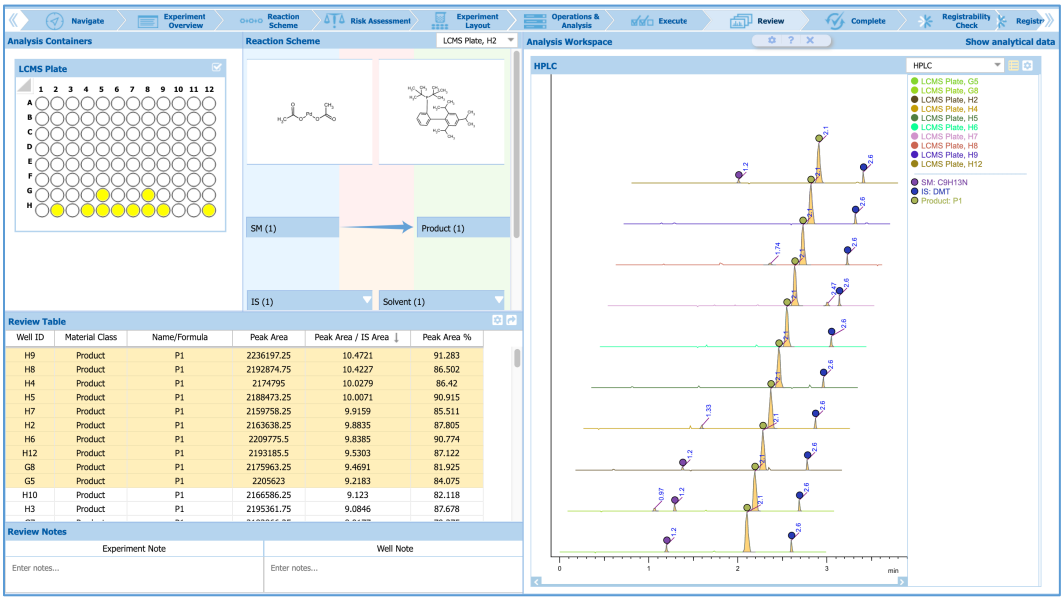


Figure 6: Dynamic stacked plot of the 10 reactions with the best product yield. Live data enables easy review and analysis of results across wells for the quality of chromatography, data processing, and optimal reaction conditions.

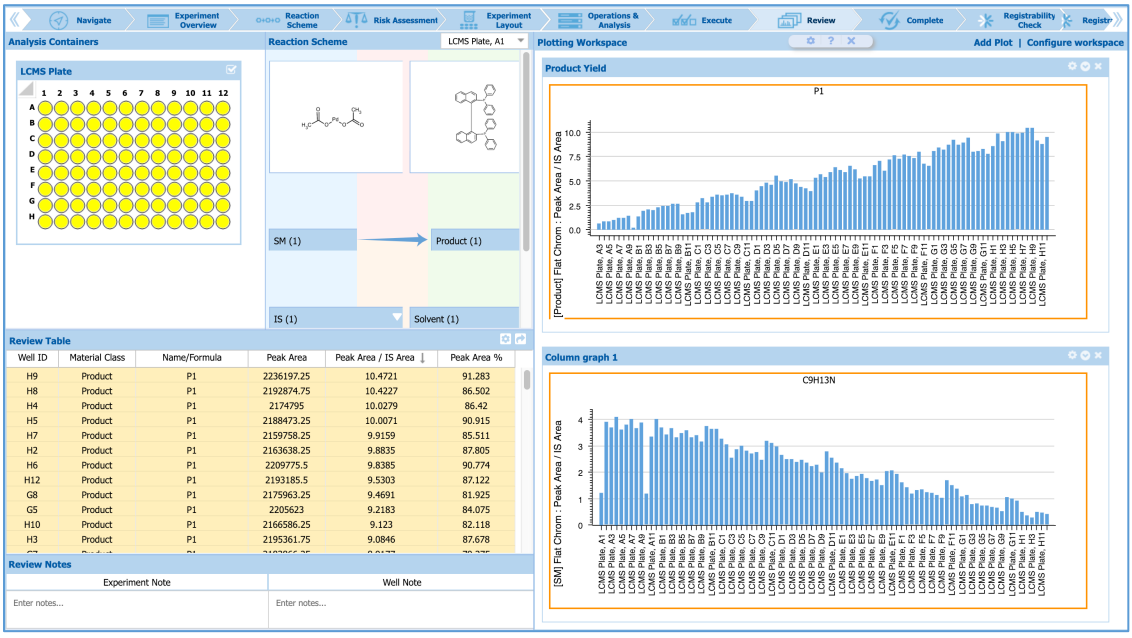
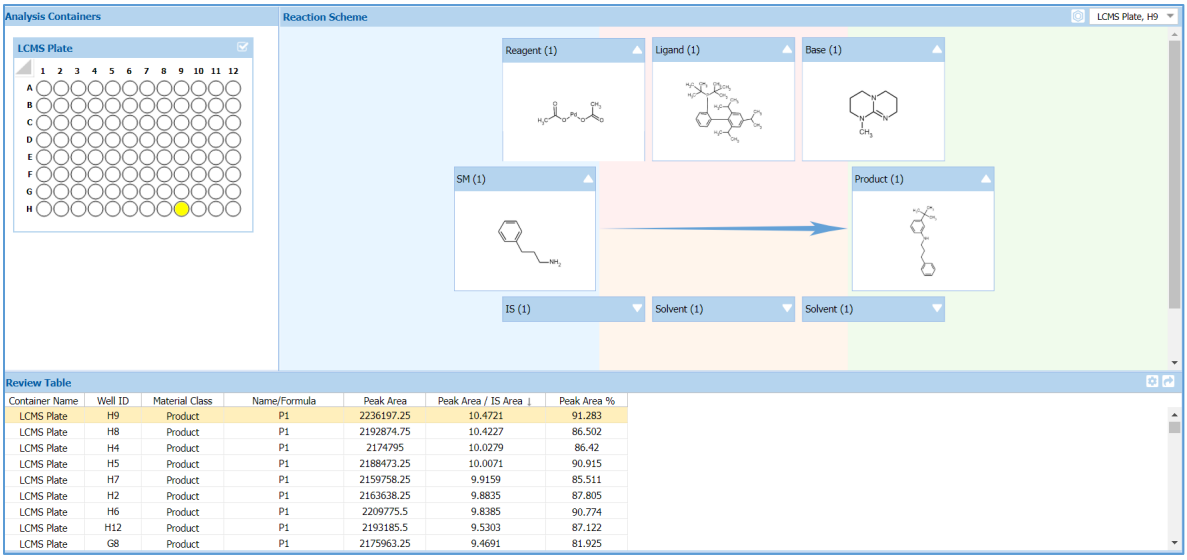


Figure 7: The plotting workspace further helps in the identification of the optimal reaction conditions suitable for scale-up. This plot shows product yield (top right) and residual starting material' (bottom right) for the entire 96-well plate.

The ability to plot results (Figure 7) further supports quick and confident decision-making about the ideal ligand and base combinations. In this catalyst screen, wells H9, H8, H4, H5, H7, are identified as

providing the highest product yields (85–91%) and the best ligand and base combination from this catalyst screen is identified as:

- Ligand: tBuXPhos (2-Di-tert-butylphosphino-2’,4’,6’-triisopropylbiphenyl)
- Base: MTBD (7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene)



Container Name	Well ID	Material Class	Name/Formula	Peak Area	Peak Area / IS Area	Peak Area %
LCMS Plate	H9	Product	P1	2236197.25	10.4721	91.283
LCMS Plate	H8	Product	P1	2192874.75	10.4227	86.502
LCMS Plate	H4	Product	P1	2174795	10.0279	86.42
LCMS Plate	H5	Product	P1	2188473.25	10.0071	90.915
LCMS Plate	H7	Product	P1	2159758.25	9.9159	85.511
LCMS Plate	H2	Product	P1	2163638.25	9.8835	87.805
LCMS Plate	H6	Product	P1	2209775.5	9.8385	90.774
LCMS Plate	H12	Product	P1	2193185.5	9.5303	87.122
LCMS Plate	G8	Product	P1	2175963.25	9.4691	81.925

Figure 8: Katalyst D2D empowers the user to quickly and confidently identify the best ligand-base combination for the experiment. The review table has been ordered by product peak area for convenience.

Conclusion

Efficient design, planning, execution, and analysis of catalyst screening experiments can present a significant productivity challenge to process chemistry groups. Katalyst D2D provides scientists with a single application interface to effectively identify catalytic conditions for process routes of interest as efficiently as possible.

References

1. Katalyst D2D, version 2018.2, Advanced Chemistry Development, Inc., Toronto, On, Canada, www.acdlabs.com, 2019