Practical High-Throughput Experimentation for Chemists

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S Supporting Information

ABSTRACT: Large arrays of hypothesis-driven, rationally designed experiments are powerful tools for solving complex chemical problems. Conceptual and practical aspects of chemical high-throughput experimentation are discussed. A case study in the application of high-throughput experimentation to a key synthetic step in a drug discovery program and subsequent optimization for the first large scale synthesis of a drug candidate is exemplified.
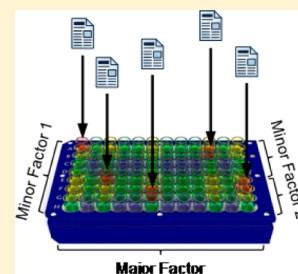
KEYWORDS: High-throughput experimentation

High-throughput experimentation (HTE) is a technique that allows the execution of large numbers of experiments to be conducted in parallel while requiring less effort per experiment when compared to traditional means of experimentation. These tools and techniques have their origins in the field of biology in the 1950s[1] and have matured to the point that experiments are now routinely executed for high-throughput screening in 3456-well microtiter plates; HTE has become standard practice in biology laboratories across the world. In contrast, the state of the art in chemical HTE is far less developed, and the techniques much less frequently employed. While protocols for running chemistry experiments in 96-well format have become well-developed, few efforts have been successful in continuing to reduce the scale and increase the density of chemical experiments.[2] In addition, only a select few industrial laboratories routinely practice chemical HTE, and the technique is extremely rare in academic settings. This distinction between the degree of HTE utilization and sophistication in biology and chemistry can be attributed mainly to engineering challenges; while biology and biochemistry experiments are typically conducted in aqueous media at or near room temperature, chemical experiments may be carried out in many solvents over a much broader temperature range, and often involve heterogeneous mixtures that are difficult to array and agitate in a wellplate format. The use of volatile organic solvents also introduces additional challenges of material compatibility and evaporative solvent loss.

When employed in chemical research, HTE is frequently used to examine arrays of reaction conditions to quickly determine the preferred catalyst, reagents, and solvents to use for a given transformation.[3,4] In this context, these tools are equally powerful for optimizing individual steps in a total synthesis or as a driver for discovery of novel methodology.[5−8] Another powerful application of HTE combines arrays of reactants under a small set of conditions to make large collections of diverse products, with known applications in medicinal chemistry[9] or materials science.[10] These tools have also been used to demonstrate generality and functional group tolerance of new reactions,[11,12] elucidate reaction mechanisms,[13] determine solubility,[14] evaluate process adsorbents,[15] and identify crystalline polymorphs and salts of organic molecules.[16]

HTE accelerates experimental work in several critical dimensions. Grouping common operations saves time by minimizing the number of operations to be performed, whether they are tip changes on a manual pipette or tip washes on a liquid handling robot. As a corollary to this efficiency, dispensing reagents as stock solutions accelerates experimental setup. While reagents can be weighed directly when setting up a small number of traditional experiments, solid handling is challenging to perform on large arrays of experiments. Liquid handling is both fast and accurate, but neither manual nor automated manipulation of solid reagents qualifies as such. Finally, employing predispensed libraries of common catalysts and reagents is a powerful way to accelerate experimental setup because it allows the effort required to assemble the largest dimensions of experimental matrices to be decoupled from the effort required for a given experiment.

In an era of declining resources and increasing demands in the research lab, there are several compelling reasons to consider HTE when conducting chemical research. First, novel synthetic approaches that require forming chemical bonds in unprecedented ways inevitably require significant amounts of experimentation in order to achieve breakthrough new discoveries. These tools allow a scientist to "go big" and run orders of magnitude more chemistry than has been traditionally

possible. Second, material limitations frequently restrict the breadth of conditions evaluated during a given step of a synthesis. The miniaturization inherent in HTE allows a scientist to "go small" and run small arrays of experiments where limited amounts of precious scaffolds traditionally would have allowed only one or two experiments. Finally, many chemical transformations require routine reagent, solvent, and parameter screening in order to discover conditions that are good enough to push material forward to access the transformation of interest. HTE allows a scientist to "go fast" and execute a single array of carefully chosen conditions in order to spend less time on routine synthesis and more time on research.

Herein, experiences gained over 15 years of HTE in the Catalysis Laboratory in the Department of Process Research & Development at Merck & Co., Inc., Kenilworth, NJ, USA are presented. Illustrative examples have been carefully chosen to inspire, rather than prescribe, how HTE can be used to solve complex problems in synthesis. Furthermore, the intent is to present HTE not just as a tool for expert users in highly automated laboratories, but as an enabling approach to reaction discovery, development, and optimization that can be broadly employed by all chemists conducting research.

■ RATIONALLY DESIGNING LARGE ARRAYS OF EXPERIMENTS

Traditional chemical experimentation frequently begins with a survey of the relevant literature followed by winnowing down potential reaction conditions to a small number of ideas that can be practically tested in the lab (Figure 1). These reactions
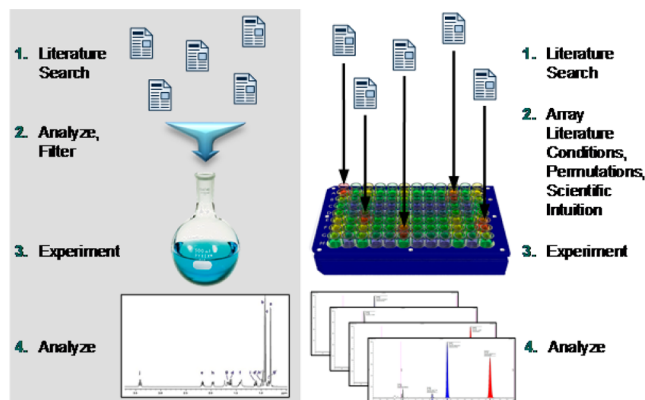

Figure 1. Traditional experimentation vs rational HTE.

are then carried out and worked up, and products are isolated and identified or confirmed. When initial hypotheses are correct, this method works well; however, when attacking difficult problems, this cycle of experimentation is frequently iterated many times before suitable conditions can be found or the researcher concludes the approach is not feasible. In contrast, when performing HTE, one can compose an array of experiments consisting of many (or all!) of the relevant literature conditions. In addition to direct testing of literature conditions, the permutations of those conditions can all be examined, mixing and matching metal precursors, ligands, reagents, and solvents. Finally, the array can be augmented with one's scientific intuition, including conditions not yet known for the desired transformation. With HTE tools, this entire array of experiments can be quickly executed on microscale so

that the amount of material consumed by each individual experiment is small. Fast and quantitative analytical techniques, such as HPLC and UPLC, frequently with MS detection, are then used with minimal workup to generate results quickly. This rational, hypothesis-driven HTE is the logical extension of traditional chemical experimentation. Since the cost of setting up large arrays of experiments is minimal, HTE affords the additional rigor of being able to explicitly examine every combination of experimental parameters. In addition, there is replication inherent in the design of a rational array of experiments, and it is possible to find patterns in the results that would never be uncovered without such a wealth of data.

There have been reports of HTE tools used to rapidly screen random arrays of reactants in order to discover new or improved reactivity.[17,18] While it is true that random screening can provide breakthrough insight into advance chemical research, we believe that the true power of HTE lies in the ability to pose big questions and get big answers. In traditional experimentation, when we select a particular set of conditions from the literature to try for our chemical system, we are, in effect, postulating that our chosen single set of conditions should work well for our purposes. With HTE, interrogating an array of experimental conditions tests the hypothesis that answers to our problem lie somewhere within the chemical space bounded by our choices of ligand, metal precursor, solvent, and other reagents. In this large array, we also are afforded the opportunity to ask questions about how the nature of these reaction components affects the outcome of our chemistry, and we are rewarded with a much more detailed understanding of our chemistry with each experimental cycle.

Since HTE tools accelerate the execution of experimental arrays, we are afforded the luxury of spending more time carefully choosing their constituents. As an example, consider the reaction solvent. Chemists frequently describe solvent with broad categories, such as polar aprotics, alcohols, and so forth, without necessarily considering the subtle differences between solvents of those categories. However, numerical parameters such as dielectric constant and dipole moment describe solvent properties and can assist in choosing solvents to maximize the breadth of chemical space examined in an array (Figure 2). Dielectric constant describes how well a solvent separates charges and is related to the solubility of ionic reagents or the
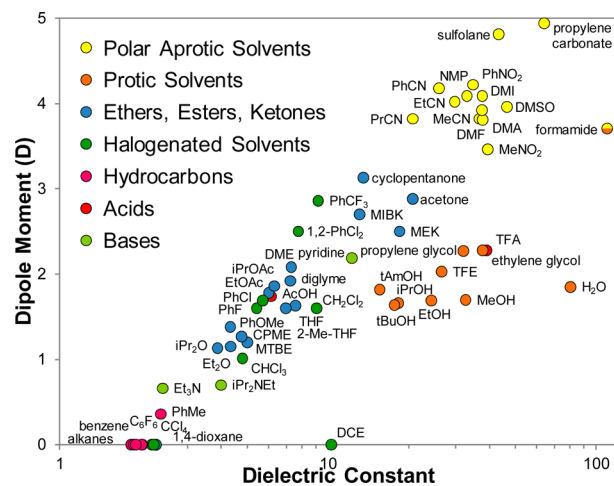

Figure 2. Plot of dipole moment vs dielectric constant for commonly used solvents.

stability of ionic intermediates. Dipole moment describes internal charge separation in solvent molecules and can be related to how nucleophilic or coordinating the solvent is. These properties are of considerable interest for metal-mediated reactions. For example, when using cationic rhodium catalysts to perform homogeneous hydrogenation, solvents with high dielectric constant can solubilize or stabilize the ionic catalyst species, but solvents with high dipole moment may coordinate to the electrophilic metal center and inhibit reactivity. For this reason, alcohols frequently perform well in these reactions, since they have a high dielectric constant but a moderate dipole moment. If one were choosing solvents for an array of such reactions, it may be useful to bias the array with more members with these desired properties and fewer members with high dipole moments or low dielectric constants.

Large arrays of experiments enabled by HTE also afford the opportunity to include negative controls and null hypotheses. We have found great value in including these conditions in order to test the limits of our understanding of chemistry. For example, while investigating improved conditions for Pd-catalyzed cyanation of aryl chlorides, we found an [(allyl)-PdCl]$_2$/X-Phos catalyst that gave high yields when run inside a glovebox, but consistently poor performance using standard Schlenk techniques (Figure 3).[19] An array of duplicate reactions
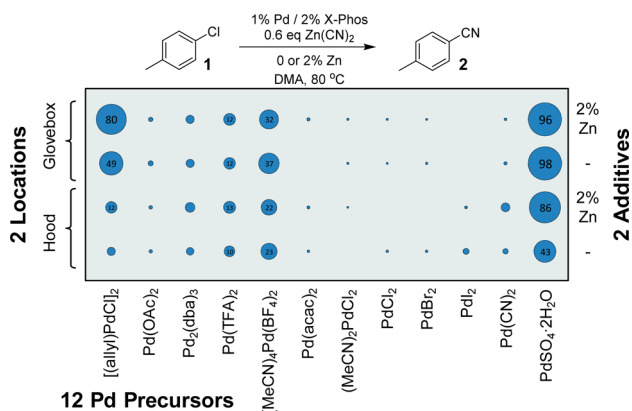

Figure 3. Pd precursor screen for the cyanation of aryl chlorides. Size of circles indicates yield determined by HPLC analysis.

with different Pd precursors was assembled in the glovebox and run in either the glovebox or sealed and heated in an oil bath outside the glovebox. Pd precursors traditionally used for cross-coupling gave low yield, as did palladium(II) halides. However, PdSO$_4$·2H$_2$O, included as a negative control, since its very low solubility in organics was thought to preclude useful reactivity, conferred high reactivity. We postulated that this surprising result may be due to sulfate assisting in transmetalation processes to give high reactivity, despite the limited amount of catalyst in solution. This unexpected discovery moved the research in a different direction and evolved into soluble Pd(OAc)$_2$/H$_2$SO$_4$ conditions that consistently gave robust reactions at low catalyst loadings.

At first glance, it may seem that HTE gives chemists the ability to run more reactions than it is possible to have ideas. However, when considering a rationally constructed array that explicitly examines all combinations of its factors, the size of arrays can multiply quickly. When time or material constraints limit the size of experimental arrays, it is useful to consider the relative impact experimental factors have on the outcome. In an

initial study, the most important factor merits the largest dimension of the array, while minor factors are assigned progressively smaller fractions. As an example, consider the Heck coupling of methyl vinyl ketone with aryl bromide 3 (Figure 4). It was postulated that the base sensitivity of product 4 might be responsible for the poor yield under standard Heck conditions. Since the nature of the ligand has the largest impact
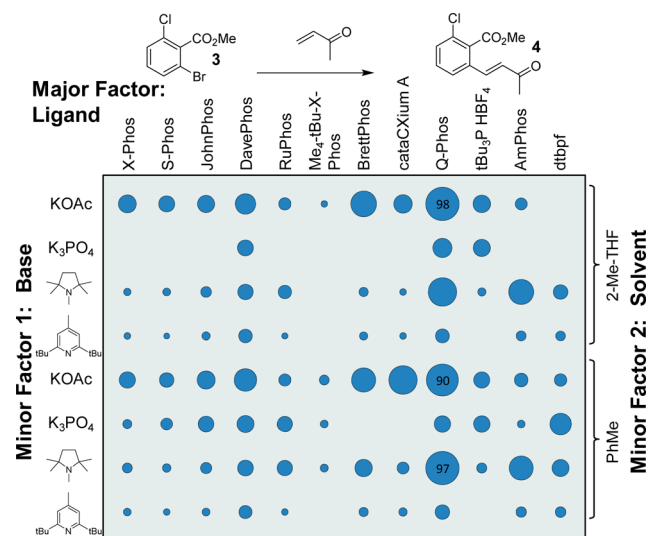

Figure 4. Pd-catalyzed Heck coupling of methyl vinyl ketone. Size of circles indicates yield determined by HPLC analysis.

on the outcome of Pd-catalyzed cross-coupling, we chose 12 ligands as the largest dimension of the array. We selected 4 bases as the next largest dimension, including hindered or weaker bases to mitigate potential base sensitivity. Finally, the smallest dimension consisted of two solvents. We discovered that Q-Phos was the optimal ligand, and indeed, the weak base KOAc was required for high yield. If continued optimization had been required for this chemistry, then the minor factors in this experiment could have become major factors in the next array.

■ EXECUTING AND ANALYZING LARGE ARRAYS OF EXPERIMENTS

For most microscale HTE experiments, 100 μL reactions in 8 mm × 30 mm glass vial inserts in metal 96-well metal microtiter plates provide an ideal balance of small scale (to minimize material requirements) and ease of use for both manual and automated reaction setup. At this scale, only 10 μmol of substrate per well is required at 0.1 M concentration. When material limitations restrict the number of experiments that can be performed, 20 μL reactions in 4 mm × 21 mm glass vial inserts may be used, which serves to cut material requirements 5-fold. These wellplates, associated consumables, and light sources for high-throughput photochemistry are commercially available.[20] On a small scale, adequate exclusion of atmospheric oxygen and/or water may be critical; inert-atmosphere gloveboxes are the most convenient means of ensuring good inertion of the reaction atmosphere. For reactions run under reactive gases, such as hydrogen or carbon monoxide, plates can be sealed into pressure vessels in the glovebox and then connected to the appropriate gas supply.[21]

As highlighted previously, the most efficient means of introducing materials to microscale arrays is via liquid handling

of stock solutions. Neat liquids, solutions, and homogeneous suspensions or slurries can be dosed rapidly and accurately; however, immiscible liquid−liquid mixtures do not transfer well. Many early chemical HTE approaches focused on automated liquid handling, but liquid handling robots require significant capital investment and significant training to use.[22−24] While automated liquid handling is our preferred method for duplicating screening libraries, we have found that manual liquid handling offers several advantages for setting up the majority of HTE arrays. Compared to automated liquid handling robots, manual single-channel and multichannel pipettes are inexpensive, are easy to use, and confer flexibility to the experimental setup. In contrast to liquid handling, solid handling is both slow and inaccurate. While automated solid handling robots are available, our experience suggests that they are best suited to performing repetitive, preparative tasks such as preparing screening libraries because they are too slow to use while setting up experiments. Furthermore, different solid dispensing technologies perform better with different types of solids, and no general automated solid handling solution currently exists.

In addition to having tools for fast and accurate dosing of materials to experimental arrays, it is also useful to quickly and quantitatively remove chemicals from wellplates. Removal of volatile solvents can be accomplished with a vacuum centrifuge or an array of nitrogen needles. The ability to remove solvents allows for formation of catalysts in solvents optimum for metal−ligand complex formation independent of the solvents to be evaluated for the desired reaction. Undesired solids can be removed with wellplate-format filter plates under vacuum or in a centrifuge, or plates can be centrifuged and the supernatant removed by careful pipetting.

Ensuring adequate, uniform mixing of arrays of reactions is important for heterogeneous reactions. While small 24-well arrays of reactions can be stirred on a standard rotary stirplate, 96-well plates suffer due to insufficient magnetic field across the array. As an alternative, magnetic tumble stirring is efficient for stirring microtiter plates, and can be combined with various plate heaters and coolers.[20] Vortex mixing also works well for agitating HTE arrays, but most commercial vortex mixers offer limited options for temperature control.

Finally, fast analytical techniques allow for efficient analysis of HTE arrays. Reverse-phase HPLC or UPLC with modern stationary phases and fast gradients offers general-purpose utility for the determination of conversion or yield for routine analysis of ordinary pharmaceutical intermediates, with analysis times on the order of a few minutes per sample.[25] UV detection is generally applicable, since most compounds contain chromophores, and MS analysis is helpful for the identification of new compounds and unknown byproducts.[26] For compounds without chromophores, fast GC analysis or HPLC-CAD[27] can be used. Rapid determinations of enantiomeric excess are enabled by fast SFC analysis with chiral columns.[28] When even faster analysis is required, advanced techniques, such as sample pooling and MISER, can further decrease time cycles.[2,29,30] In all cases, it is critical to have instruments equipped with wellplate autosamplers, such that aliquots of reaction mixtures can be transferred efficiently via multichannel pipettes and diluted into daughter plates for analysis.

■ CASE STUDY: TANDEM HECK−SUZUKI REACTION

During the course of a drug discovery program, medicinal chemistry required access to 3,3-disubstituted oxindoles such as

11.[31] These key core structures were initially prepared through oxindole alkylation (Scheme 1). However, commercial

Scheme 1. Synthesis of 3,3-Disubstituted Oxindoles
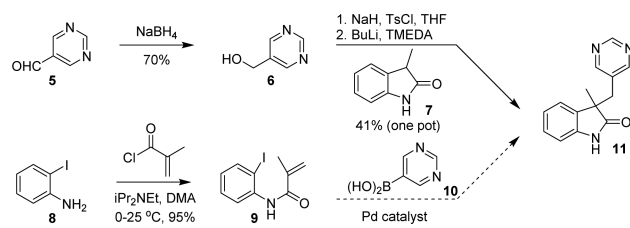
availability of substituted benzylic electrophiles was low, and their multistep synthesis often proceeded in low yield. A proposed alternative approach involved a tandem Heck−Suzuki coupling to quickly assemble the core structure from readily available building blocks. While tandem Heck-cross coupling reactions to form oxindoles are known, these methods require substitution on nitrogen for successful reaction.[32] Since installation and removal of a protecting group was not conducive to a streamlined synthesis of candidates for SAR studies, we set out to develop a protecting group-free tandem Heck−Suzuki reaction for the synthesis of 3,3-disubstituted oxindoles.

We began our investigation with an array of catalysts formed from Pd₂dba₃ and 12 ligands known to facilitate many types of Pd-catalyzed cross-coupling reactions (Figure 5). Additional
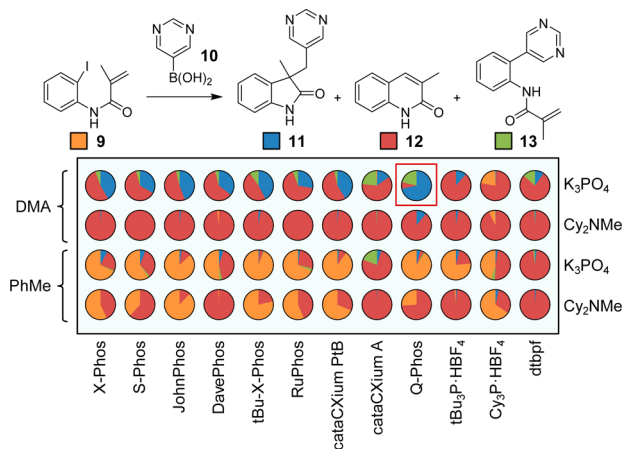

Figure 5. Initial screen of tandem Heck−Suzuki conditions. Area of pie slices indicates percent conversion determined by HPLC.

factors examined were base (inorganic K_3PO_4 vs organic Cy_2NMe) and solvent (polar aprotic DMA vs nonpolar PhMe). In addition to desired product 11, significant quantities of regioisomeric Heck byproduct 12 and direct Suzuki-coupling byproduct 13 were observed. While many conditions gave low reactivity or favored byproduct 12, we were delighted to observe a single reaction (Q-Phos,[33] K_3PO_4, DMA) that gave significant amounts of the desired product.

We next turned our attention to the minor factors from the first experiment: base and solvent. A large array of bases and solvents were examined with the Pd₂dba₃/Q-Phos catalyst (Figure 6). Surprisingly, isopropanol provided over 95% conversion to 11 with inorganic bases Cs_2CO_3 or K_3PO_4. While this solvent may not typically be chosen for a cross-coupling reaction due to potential reduction[34] or C−O
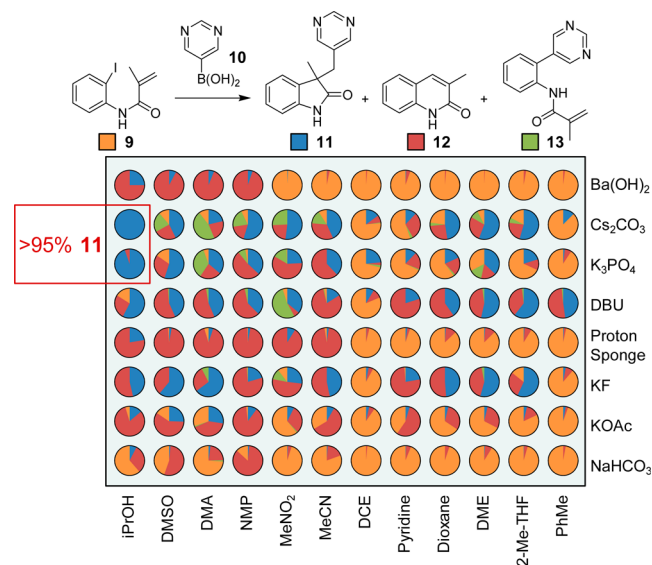
Figure 6. Examination of solvents and bases. Area of pie slices indicates percent conversion determined by HPLC.

coupling byproducts,[35] we postulate that in situ formation of boronate esters in alcohol solvent was beneficial for this transformation by modulating relative rates of Heck vs Suzuki reactions.

These conditions were then used by the medicinal chemistry team to prepare a series of analogues for SAR studies. However, as the program matured and a single candidate was advanced into preclinical development, it was apparent that further optimization was necessary in preparation for a kilogram scale delivery. Several issues needed to be addressed: (1) variability in performance when using different lots of $Pd_2(dba)_3$, (2) prohibitive cost of the ligand Q-Phos, which had only recently been commercialized and was not readily available on large scale, and (3) reproducibility issues associated with reaction impurity profiles. We tackled these issues with a series of smaller arrays of experiments (Figure 7).

We first examined an array of alcohol solvents and Pd precursors in the presence of either Cs_2CO_3 or K_3PO_4 base and demonstrated that replacing Pd_2dba_3 with $Pd(OAc)_2$ gave
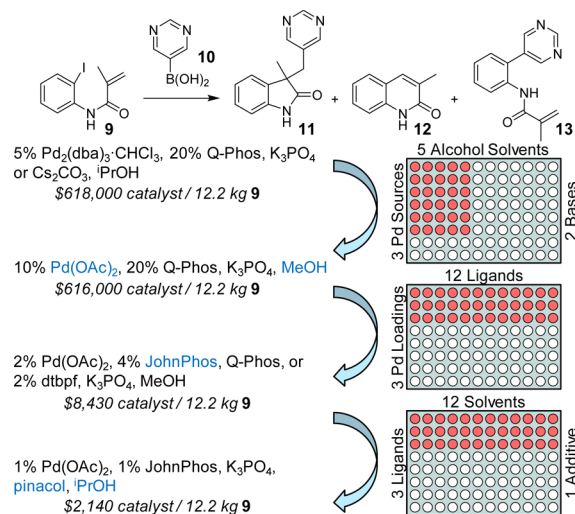
improved performance, with K_3PO_4/MeOH giving the cleanest reaction profile. With optimized conditions, we revisited ligand screening at several catalyst loadings and showed that in addition to Q-Phos the ligands JohnPhos and dtbpf also provided high yield of the desired product at loadings as low as 2 mol % Pd. Finally, we examined these catalysts in different solvents in the presence of stoichiometric pinacol to intentionally esterify the boronic acid. The optimal conditions identified were 1 mol % $Pd(OAc)_2$, 1 mol % JohnPhos, 1.5 equiv boronic acid, 1.8 equiv pinacol, 2 equiv K_3PO_4, iPrOH, 80 °C, giving 91% yield of the desired product. These conditions were robust and reproducible, and were executed on 12.2 kg scale for the synthesis of TROX-1 (16)[36] (Scheme 2).

Scheme 2. Large Scale Synthesis of TROX-1
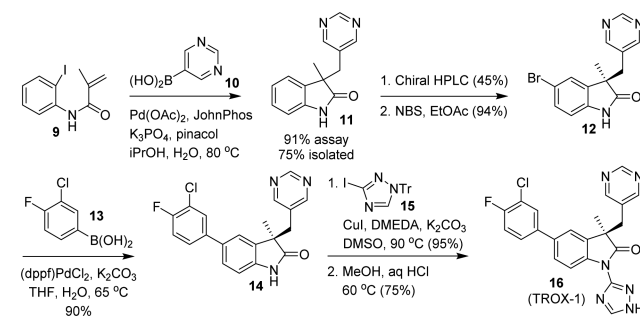
The foregoing example illustrates the power and versatility of HTE for chemical problem-solving. When presented with the challenge of finding conditions for an unprecedented tandem Heck−Suzuki cyclization on unprotected 2-haloaryl acrylamides, HTE rapidly led to a "needle in a haystack" result that was readily optimized through further application of HTE to deliver conditions adequate for SAR exploration and library synthesis. When medicinal chemistry success led to the need to deliver large quantities of a preclinical candidate from this oxindole series, focused HTE arrays quickly led to highly optimized conditions that robustly gave the desired product in high yield on kilogram scale.

■ CONCLUSION

Fifteen years of high-throughput experimentation applied to problems in process and medicinal chemistry at Merck & Co., Inc., Kenilworth, NJ, USA has proven the tremendous potential of this technique for solving even the most daunting synthetic challenges. The power of these tools lies in their ability to enable chemists to rapidly execute large arrays of rationally designed experiments to test multidimensional hypotheses and collect large data sets. Our experience has taught us that even simple, inexpensive tools such as manual pipettes and 96-well plates can make step changes in research productivity; the next step is broad acceptance and adoption of HTE by the synthetic chemistry community. We strongly believe that widespread application of these tools holds the potential to fundamentally change the way synthetic chemists solve problems across industry and academia, leading to profound increases in research output and an acceleration of the pace of development of the entire field of organic chemistry.

Figure 7. Optimization of tandem Heck−Suzuki coupling.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchemlett.7b00165.

List of suppliers of HTE tools and consumables; supplementary references on tandem Heck–cross coupling reactions. (PDF)

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Notes

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ABBREVIATIONS

CAD, charged aerosol detector; GC, gas chromatography; HPLC, high-performance liquid chromatography; HTE, high-throughput experimentation; MISER, multiple injections in a single experimental run; MS, mass spectral detector; SAR, structure–activity relationships; SFC, supercritical fluid chromatography; UPLC, ultraperformance liquid chromatography; UV, ultraviolet absorbance detector

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