Microreactors

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An Integrated Microreactor System for Self-Optimization of a Heck Reaction: From Micro- to Mesoscale Flow Systems**

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Continuous flow processes offer several advantages over traditional batch synthesis including ease of scale up[1,2] and the ability to run reactions safely at extreme pressures and temperatures.[3–6] Microreactors in particular have been shown to have superior heat and mass transfer rates,[7–9] providing precise control of reaction conditions.[10] These attributes make microreactors ideal for fast reactions,[11] highly exothermic reactions,[12] explosive reactions,[13] and reactions that involve energetic intermediates.[14] The small volume capacity of microreactors has also allowed the efficient development of more sophisticated continuous flow reactions on increasingly complex molecular targets since they greatly reduce the quantities of materials needed to optimize reaction conditions.[8,15–20] However, the specialized equipment required for microreactor flow systems also increases the difficulty of screening reaction conditions in parallel as is commonly performed in batch. Thus, developing efficient strategies to optimize reaction conditions in a series of consecutive experiments is particularly valuable for microreactors. Towards this end we have developed a self-optimizing microreactor system that uses previous reaction data to efficiently select future experiments. This approach allows numerous parameters to be optimized simultaneously.

Several automated microreactors systems have been developed that are capable of sampling a series of predetermined reaction conditions. These systems often employ a univariable approach in which only a single variable is adjusted at a time.[21] Such exhaustive searches are inherently inefficient since they are likely to gather a significant percentage of data points that are far away from the desired maximum. A more sophisticated automated microreactor system based on Design of Experiment methods has also been developed. Although this system is ideally suited for response surface modeling, the approach is less efficient in terms of the number of reactions required for an optimization.[22] Integrating feedback into the reaction optimization could significantly increase the speed and efficiency of the overall process by directing the system away from lower yielding reaction conditions.[23] Furthermore, reaction optimization results obtained in a microreactor are typically not limited by mass or heat transfer effects. Consequently, moving from optimal laboratory conditions to larger scale reactors can be more easily achieved by integrating the observed chemical understanding with established chemical engineering reactor design methods.[24–26]

Herein we describe a self-optimizing microreactor system that employs a "black-box" optimization technique directed by the Nelder–Mead Simplex Method.[27] The system was shown to maximize the yield of a Heck reaction by adjusting the equivalents of the alkene and the residence time. Upon obtaining optimized conditions in a microreactor, the reaction was scaled-up 50-fold in a mesoscale flow reactor. Reaction conditions were surveyed in the mesoscale reactor and found to be in good agreement with the yields observed in the microreactor. The optimal residence time and equivalents of alkene were then allowed to run in the mesoscale reactor for 22 reactor volumes (ca. 2 h) and upon purification the resulting isolated yield was found to be in good agreement with the online HPLC analysis.

We chose to examine the Heck reaction of 4-chlorobenzotrifluoride (**1**) and 2,3-dihydrofuran (**2**; Scheme 1) since the desired product **3** readily reacts with a second equivalent of the aryl chloride.[28] Thus, the yield of the reaction is highly dependent upon the number of equivalents of **2**. Moreover, developing flow conditions for the Heck reaction of aryl halides would be desirable since this transformation is commonly used in the synthesis of a variety of compounds[29,30] including active pharmaceutical ingredients,[31] fine chemicals,[32] and natural products.[33,34] Although several continuous flow Heck reactions of aryl halides have been reported using microreactors, these works focused on the use of heterogeneous palladium catalysts under ligandless conditions and were therefore limited to aryl iodides or activated aryl bromides as substrates.[35–41]

We began with the conditions that Fu and co-workers reported to efficiently couple deactivated aryl bromides and aryl chlorides with alkenes at room temperature. These conditions were modified to avoid generating insoluble ammonium salts and palladium black that would likely lead to clogging in a microreactor.

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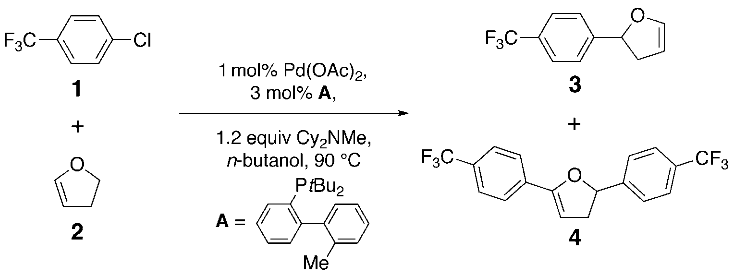

Scheme 1. Heck reaction of monoarylated product **3**. Cy = cyclohexyl.

A variety of solvents, phosphine ligands, and palladium sources were screened to find conditions to solubilize the ammonium salts and minimize formation of palladium black. The combination of palladium(II) acetate and the *tert*-butyl-MePhos ligand **A**, in *n*-butanol was found to be a highly active and stable catalyst system that did not cause clogging when the reaction was performed in a microreactor under flow conditions. The reaction reached full conversion in less than 10 minutes with 1 mol% palladium at 90 °C. At higher reaction temperatures, palladium precipitated along the microreactor channels and corresponded with a decrease in the yield of **3**. However, at 90 °C, palladium deposition was significantly slower and the reaction yield was stable over long periods of time (see Figure S2 in the Supporting Information).

The automated system maximized the yield of **3** by varying the residence time and the ratio of alkene to aryl chloride employed (Figure 1). The reaction components were loaded into three syringes. The first contained a solution of **1**, amine base, ligand **A**, and palladium(II) acetate. The second and third syringes contained neat **2** and *n*-butanol, respectively. Manipulating the flow rates of these three syringes allowed the number of equivalents of **2** and residence time to be adjusted for each experiment, although the concentration of the aryl chloride was always held constant at 1 M. This strategy could also be used to control other variables including the concentration, catalyst loading, pH value, ionic strength, and solvent composition.

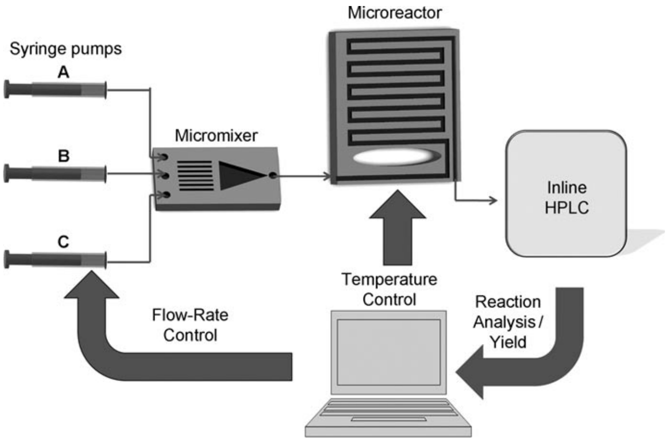

Figure 1. Automated microreactor system incorporates feedback for self-optimization of a chemical reaction. For the example Heck reaction, syringe A contained the aryl chloride, amine base, and palladium source, syringe B contained the alkene, and syringe C contained *n*-butanol.

The three solution streams were combined and mixed in an interdigital micromixer and then heated to 90 °C in a 140 μL silicon microreactor. At the outlet of the reactor, the concentration of the solution was diluted to one third with acetonitrile to prevent precipitation of the ammonium salt and for analysis by HPLC. To ensure steady-state data collection, the system was flushed for a period of approximately three residence times before HPLC analysis was initiated by the centralized control. A 2 μL sample of the reaction stream was introduced into the HPLC apparatus through an actuated six-port valve. The yield of the reaction was calculated by comparison to an internal standard.

The optimization process was directed by the Nelder–Mead Simplex Method.[27] This technique is a "black-box" optimization approach;[42–44] therefore, no a priori reaction or gradient information is required (a more detailed explanation of this method is described in the Supporting Information). This method creates an initial simplex consisting of $k+1$ vertices, where k is equal to the number of parameters or variables. In the present work, we optimized the reaction by adjusting two variables—residence time and equivalents of alkene **2**. The objective function value, the yield of the monoarlyated product in this work, is evaluated at each of these conditions and the next experimental conditions are determined by reflecting the point with the worst yield about the midpoint of the remaining k points. This sequential process continues until it has been determined that none of the possible reflections in the simplex will give a greater yield. To locate the optimum with greater accuracy, the size of the simplex contracts and the procedure is repeated until a specified termination criterion is achieved. For the experimental investigation, we chose to terminate the optimization when the greatest difference between two yields in the simplex was less than 3%. This termination criterion was chosen since error in the HPLC analysis would make it difficult to discriminate between yields that differ by less than 3%.

An upper boundary of 6.0 was placed on the equivalents of **2** because this is near the maximum concentration of alkene that can be obtained while maintaining a 1 M concentration of aryl choride **1**. Any potential reaction conditions selected by the optimization algorithm exceeding 6.0 equivalents were projected onto this upper boundary. Although the yields at this boundary line were performed and analyzed, these points were "penalized" by substituting 0% into the optimization algorithm. The use of a penalty function improves the efficiency of the algorithm by preventing the simplex from prematurely contracting or collapsing. To allow the system to find optima that are located on the boundary, this penalty function was removed after the simplex had contracted.

The first experiment for the optimization procedure was chosen at 1.0 equivalent of **2** and a residence time of 3 minutes (Figure 2, Exp. 1). This initial experimental point was selected based upon the knowledge that an observable percentage of **3** was formed at these conditions. The so-called "step-size", a tunable parameter defined as the difference

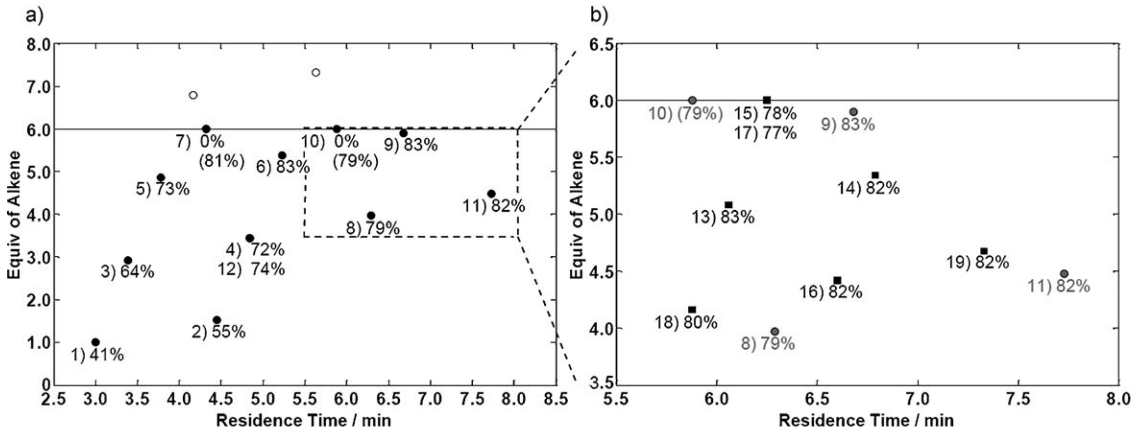

Figure 2. Optimization results for the Heck reaction depicted in Scheme 1. Results are indexed by experiment number (Exps. 1–19) and the corresponding yield of **3**. a) The data points for experiments that lie above the 6.0 equiv of alkene line (○) were projected toward the boundary (6.0 M) and penalized with a 0% yield in the optimization program. Yields at these points are parenthesized. b) The simplex size contracted to refine the location of the optimal yield (■). Reaction yield values that were obtained with the larger simplex (●) included for reference.

between the points in the simplex, was chosen so that the maximum difference between points in the simplex was a residence time of 1.5 minutes and 2.0 equivalents of **2**. We chose this step-size to perform a broad search of the parameter space without immediately exceeding the boundary on the equivalents of **2**, or sampling significantly longer residence times where iterations would reduce the throughput of the overall process.

The initial simplex (Figure 2, Exps. 1–3) indicated that the yield of **3** improves as the residence time and the equivalents of **2** were increased. The Simplex Method therefore reflected the point in the simplex with the shortest residence time and lowest number of equivalents of **2** (Figure 2, Exp. 1). This trend continued until the number of equivalents of **2** exceeded the boundary of 6.0 equivalents. This point was projected back onto the boundary, the yield was determined, and then penalized by converting the yield to 0% as previously discussed. The Simplex Method then reflected the second lowest yield and found a higher yield at a longer residence time. At the longest residence times sampled by the simplex, the yield of **3** decreased slightly, and the simplex contracted to refine the search for the optimum. This contracted simplex (Figure 2, Exps. 13–19) located the optimal conditions near a residence time of 6 minutes and 5.0 equivalents of **2**; corresponding to yield of 83%. The entire optimization process required approximately 6 g of the aryl chloride and proceeded at a rate of approximately one experiment per 20 minutes, including the time required for HPLC analysis.

The overall picture of the reaction space showed that increasing the number of equivalents of **2** resulted in an optimum yield in the region of 4.5 to 5.5 equivalents. Lower yields observed at the boundary may be a result of the fact that the alkene has nearly replaced *n*-butanol as the solvent. The yield also increased significantly with residence time until reaching a plateau around 5.5 minutes. As is true with any local search optimization routine, it is impossible to identify a single optimum when there are several yields in a region that are equivalent within experimental error. However, the ability to move quickly from an initial non-optimal point to a higher yielding region is demonstrated in this example.

Once the optimal reaction conditions were determined using smaller amounts of material in a microreactor, we wanted to demonstrate that these optimized conditions could be scaled up to obtain preparative quantities of the product. Larger production rates could be accomplished by increasing the number of parallel microreactors ("scaling out").[2] Although this approach could be feasible for small-scale production, problems such as uniform fluid distribution, process control, packaging, and the cost of multiple microreactors are significant concerns when trying to scale a reaction up by 50-fold. However, in contrast to the scale up of small batch reactors where yields can be highly influenced by transport phenomenon, the enhanced mixing and heat transfer rates in microreactors should allow the reaction to be kinetically controlled. Therefore it should be possible to operate the reaction in a mesoscale flow reactor and retain similar reaction yields, provided that the relevant features from the microreactor are mimicked on the larger scale.

To evaluate a Heck reaction of **1** and **2** at a 50-fold larger scale, a 7 mL Corning Advanced-Flow Glass Reactor module was employed. The reaction components were stored in two separate solution reservoirs. The first contained aryl chloride **1**, the amine base, phosphine ligand **A**, and palladium(II) acetate. The second reservoir contained a solution of the **2** in *n*-butanol. The solutions were pumped into the flow reactor with dual piston pumps and the residence time was controlled by varying their flow rates. The number of equivalents of alkene was adjusted by changing the concentration of **2** in the reservoir solution. Upon exiting the flow reactor the reaction stream was diluted to one seventh for analysis of the yield by HPLC.

Nine different reaction conditions were selected that encompassed the region containing the optimum yields as previously determined in the microreactor. The residence times and initiation of HPLC analysis were directed by an automated centralized control, although there was no feedback involved in the system. As shown in Figure 3, the highest yielding conditions were determined to have a residence time of 5.5 or 6.5 minutes at 5.0 equivalents of **2**. These results indicate that the optimal conditions were successfully translated from the microreactor to the mesoscale system. To validate the yields obtained by HPLC analysis, the reaction was run under the optimal conditions of 5.5 minutes and 5.0 equivalents of alkene for just over two hours, during which time 168 mL of crude solution was collected. The monoarylated product was isolated by distillation and chromatography to provide 26.9 g of **3** with a yield of 80 %. This is in good agreement with the yields determined by HPLC analysis and corresponds to an annual production rate of 114 kg/year.

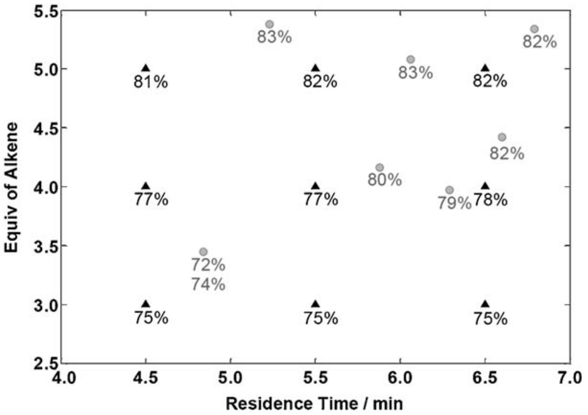

Figure 3. Yields of 50-fold reaction scale up in mesoscale flow reactor (▲). The reaction yields (●) obtained in the microreactor are shown for comparison.

In summary we have demonstrated the rapid optimization of a Heck reaction using a completely automated microreactor system with feedback control and optimization algorithms. Optimal reaction conditions in the microreactor were determined after 19 automated experiments and required a relatively small amount of starting material. The reaction was then successfully scaled up 50-fold using the optimal conditions determined by the microreactor system. The integration of automation into continuous flow systems presents an efficient new approach to reaction development. The system has the ability to perform quick and efficient multiparameter reaction optimizations in the laboratory and directly scale these results to larger systems thereby reducing process lead times. Additional advancements of this technology include the development of more sophisticated optimization techniques, the protocols to automate, optimize, and scale-up biphasic reactions, and the logic necessary to automate and optimize multistage microchemical processes.

Experimental Section

A custom fabricated silicon micoreactor was used for the automated optimization and was created using a standard photolithography and deep reactive ion etching (DRIE) techniques, respectively. The channel dimensions of the microreactor were 400 × 400 μm. Reactor temperature was measured with a thermocouple and controlled by adjusting the power cycle of a thermoelectric (TE) module.

A 7 mL Corning Advanced-Flow Glass Reactor was used for the mesoscale reaction. The channels of the reactor correspond to 0.7 mm in depth and 4 mm in width. A circulating temperature bath pumped water at 15 L min^{-1} through the integrated heat exchanger to maintain a reactor temperature of 90 °C. To ensure a high degree of mixing, a commercial HPLC gradient mixer that was packed with stainless steel ball bearings was added immediately upstream of the reactor. Specific details of equipment and work available in the Supporting Information.

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