RESEARCH ARTICLE

CHEMISTRY

Reconfigurable system for automated optimization of diverse chemical reactions

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Chemical synthesis generally requires labor-intensive, sometimes tedious trial-and-error optimization of reaction conditions. Here, we describe a plug-and-play, continuous-flow chemical synthesis system that mitigates this challenge with an integrated combination of hardware, software, and analytics. The system software controls the user-selected reagents and unit operations (reactors and separators), processes reaction analytics (high-performance liquid chromatography, mass spectrometry, vibrational spectroscopy), and conducts automated optimizations. The capabilities of this system are demonstrated in high-yielding implementations of C-C and C-N cross-coupling, olefination, reductive amination, nucleophilic aromatic substitution (S_NAr), photoredox catalysis, and a multistep sequence. The graphical user interface enables users to initiate optimizations, monitor progress remotely, and analyze results. Subsequent users of an optimized procedure need only download an electronic file, comparable to a smartphone application, to implement the protocol on their own apparatus.

Chemists invest substantial time in repetitive experimental tasks, such as reaction monitoring and iterative optimization. These activities limit the effort they would otherwise direct toward innovation and creativity and, in turn, inhibit the pace of discovery and development in fields that depend upon molecular synthesis (*1*–*3*). Here, we describe an integrated, automated approach to mitigate these challenges.

Critical in our investigations was the use of continuous-flow synthesis (*4*). The standard for commodity chemical manufacturing, this approach has received substantial attention in the past decade for its implementation in the synthesis of many classes of complex organic molecules, including pharmaceuticals (*1*, *5*–*8*). Four years ago, the end-to-end, fully integrated continuous manufacturing of a formulated pharmaceutical (aliskiren) was accomplished in a bespoke system designed for a single specific purpose. Subsequently, several technological and chemical advances enabled the creation of a compact (1.26 m^3) reconfigurable system for the end-to-end synthesis, purification, and formulation of four different pharmaceuticals. Interchanging the system among the pharmaceuticals involved designing and developing a synthetic route, selecting the appropriate types and sizes of reactors, reassembling the hardware, and optimizing the overall process (*9*, *10*). Recently, a team from Eli Lilly described a continuous manufacturing process to support phase 1 and 2 clinical trials of an active pharmaceutical ingredient (*11*).

The opportunities offered by flow synthesis in earlier stages of chemical discovery and development also have attracted major attention (*2*, *3*). Automated peptide and oligonucleotide synthesis revolutionized protein chemistry and molecular biology by providing scientists rapid access to complex biomolecules (*12*, *13*). More recently, Burke and co-workers developed an approach that uses a cross-coupling reaction to produce milligram quantities of organic molecules by an iterative, deprotection-coupling-purification sequence (*14*). A modular Vaportec-based approach by Seeberger streamlined the divergent multistep syntheses of five active pharmaceutical ingredients (*15*), and systems developed by Ley feature monitoring and control of multistep syntheses of several specific molecular targets (*16*, *17*). Multiple studies of automated optimization (*18*–*22*) have demonstrated the utility of continuous-flow and droplet systems in identifying optimal reaction conditions and catalysts for selected reactions. Advances in high-throughput experimentation (HTE) have shown that collections of molecules can be accessed in reduced time (*23*, *24*). For example, researchers at Eli Lilly demonstrated that automation of batch processes can enhance the efficacy of HTE and accelerate assaying of a library of potential biological modulators (*25*). Very recently, researchers at Pfizer reported a continuous-flow droplet platform capable of screening >1500 reagent combinations for a particular reaction as exemplified by a Suzuki-Miyaura coupling (*26*).

All of the above important advances are tailored to specific chemical reactions and/or targets. That is, the systems were not conceived with the flexibility to perform a varied array of reactions without some measure of redesign or reoptimization. Therefore, we aspired to create a compact, fully integrated, easily reconfigurable, benchtop system that enables automated optimization of a wide range of chemical transformations. During the initial investigations of such a system, we recognized that several challenges would need to be addressed. These include the chemical compatibility of components and pumping mechanisms; development of a unified, modular system for truly plug-and-play operation; appropriate software for system control and real-time monitoring (using established analytical methods) for automated feedback optimization; and ultimately, integration into a single, small-footprint platform that requires little user expertise with flow chemistry. Presented herein is the realization of these goals in a lab-scale, automated, and reconfigurable continuous-flow synthesis platform, demonstrated in single-step and multistep sequences encompassing several of the most widely used reactions in organic chemistry.

System concept and design

The system (Fig. 1) was designed to simplify labor-intensive chemical experimentation, in a manner similar to the way gas chromatography and high-performance liquid chromatography (HPLC) allow rapid automated analysis of samples with minimal technical training. To do so, we targeted the development and integration of three capabilities: hardware components that perform the syntheses and purifications, in-line analytical technologies that monitor reaction progress, and a user interface that provides software control and monitoring. The resulting system would thus be reconfigurable and perform a wide range of chemical reactions. Users would select the appropriate analytical instrument for a given optimization, and user-friendly software based in MATLAB and LabVIEW would provide control of both the system and the analytical instrument. This design would additionally offer the user a trio of modes to operate the system: (i) automated optimization of a specific reaction or sequence of reactions; (ii) synthesis of a range of substrates under user-selected conditions, for example, to investigate the scope of the transformation under conditions obtained from an optimization; (iii) or scale-up of a selected synthesis under conditions obtained from a previous optimization.

We aimed for chemically compatible plug-and-play reaction components that would enable rapid realization of different chemical transformations on a general platform providing the

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necessary fluid and temperature control and having an intuitive graphical user interface with robust optimization algorithms. Realization of the goal of plug-and-play use of the system presented, perhaps, the greatest challenge. In principle, one could combine commercial technologies (pumps, reactor tubes, in-line separators, among others) for a particular optimization, but this approach would offer only a minimal enhancement in ease of use, and would require a large footprint. Rather, we desired a system wherein only reactor modules and separators would be attached by the user in a matter of seconds, without the need to reconfigure pumps, tubes, or other flow components. This versatility was achieved by the development of a universal bay (Fig. 1B), a standardized and flexible interface that can host any type of reaction module necessary for the particular chemistry being performed. The present system comprises five such bays, and six different modules have been developed thus far: a heated reactor (up to 120°C), a cooled reactor (to −20°C), a light-emitting diode (LED)–based photochemistry reactor, a packed-bed reactor (for solid supported reagents and catalysts, as well as passive mixing), a membrane-based liquid-liquid separator (purification via extraction), and a bypass (for reagent addition in a minimal volume, mixing, or unused bay). The volume of each reactor ranges between 215 and 860 μl, depending on the internal diameter of the disposable PFA tubing used. Each bay is fed by a M6 Vici pump, with the exception of bay 1, which is connected to two pumps (Fig. 1B). In total, up to six different solutions containing reagents and/or solvents can be delivered into the system. The complete platform is contained within a small footprint and a total volume of 0.22 m^3 [0.61 m (width) × 0.86 m (length) × 0.41 m (height)].

To augment the versatility and enable intuitive use of the system by those with only minimal expertise, we designed a simple graphical interface (Fig. 1D, details of the user interface and automation scheme provided in figs. S8 and S10, and accompanying text). Automated optimization is enabled by integrating continuous reaction monitoring and precise control of the key reaction parameters using two pressure sensors, two flow meters, one phase sensor, five infrared (IR)–based temperature sensors, and two cameras for web-based remote monitoring. Several in-line analytical methods can be used with the system to enable reaction monitoring and subsequent autonomous optimization. Although HPLC provides the best balance of generality and instrument cost, IR spectroscopy (Mettler Toledo ReactIR), Raman spectroscopy (Marqmetrix Raman BallProbe), and mass spectrometry (Advion MS with electrospray ionization) are also compatible (*27*, *28*). The control software behind the user interface continuously analyzes and records the data received from these devices.

Many optimization algorithms may be used with the system, but we have found that the stable noisy optimization by branch and fit [SNOBFIT (*29*)] algorithm provides a convenient means for global optimization of single- or multistep processes without the need for a theoretical model. This agnostic, "black-box" approach

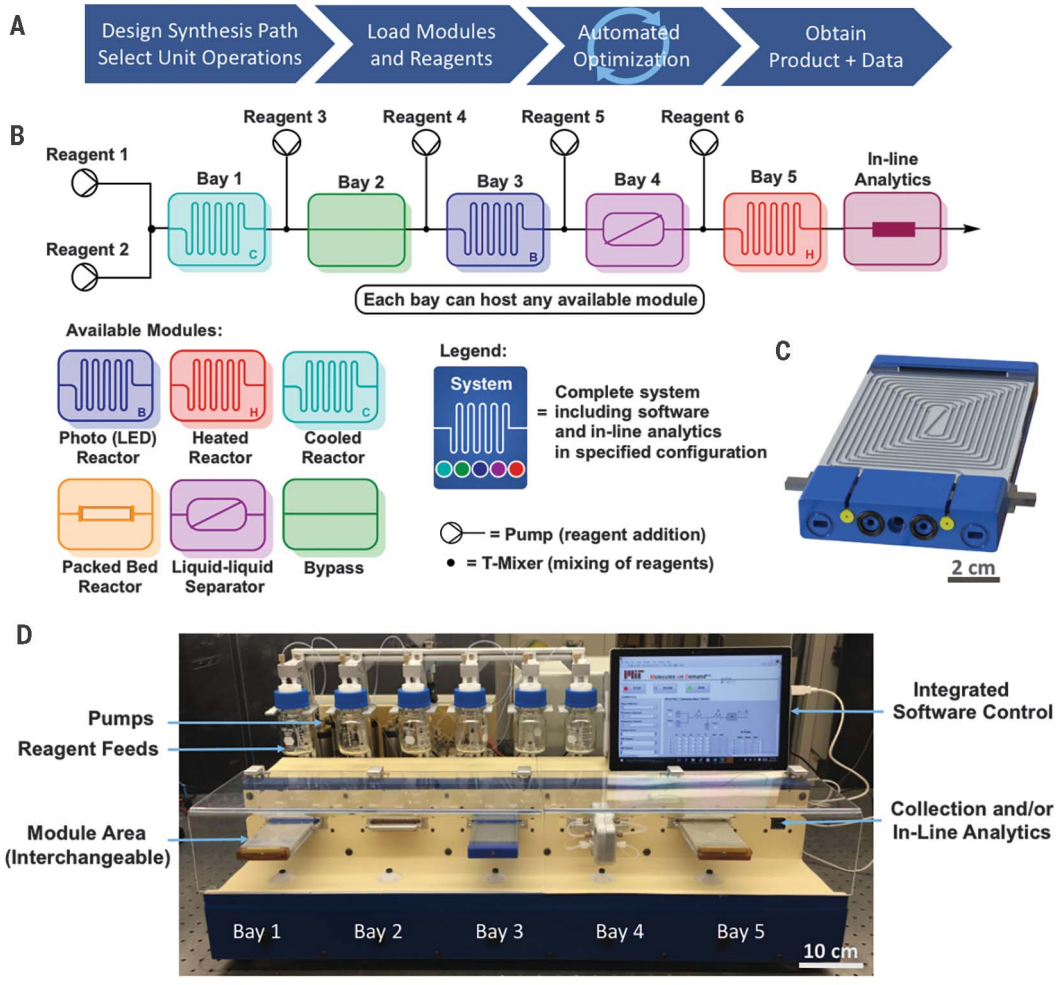

Fig. 1. Plug-and-play, reconfigurable, continuous-flow chemical synthesis system. (**A**) General four-step protocol for using the system. (**B**) Representative configuration of the components in the system. (**C**) CAD (computer-aided design) representation of the LED reactor; shown is a view of the end that attaches to a universal bay on the system. See figs. S2, S4, and S5 for details of the fluidic and electrical connections in the universal bay. (**D**) Schematic representation of the configuration shown in (B) and available modules.

provides generality and flexibility to the system (*30*, *31*) by performing local optimizations around the best conditions while continuously searching other, more distant regions to ensure that a global (rather than local) optimum is found. Alternatively, faster optimization procedures could be implemented, but with a trade-off in requiring prior knowledge of the system and an attendant loss of generality (*31*).

Automated optimization of chemical transformations

We began our tests of the system with a Paal-Knorr pyrrole synthesis. In addition to being a classic method for assembling important heterocycles, it provided us the twofold opportunity to compare the performance of the system with others we had investigated (*28*) and also to validate a suite of analytical methods (HPLC, MS, IR, and Raman; see the supplementary materials for details). Subsequently, these activities also enabled us to evaluate the portability of the platform by performing the same automated optimization in two different laboratories. To this end, after optimization of a Paal-Knorr pyrrole synthesis (see supplementary materials) in one laboratory (Jensen), the system was transferred to another (Jamison), wherein the optimization converged independently on the same reaction conditions. In this exercise, only the platform and the software were transferred between the groups; two different HPLCs were used, providing additional validation of the flexibility and generality of the system.

We next evaluated the generality and ease of use of the system described above. As thousands (5^6) of configurations of reactor modules are possible, we reasoned that the system should have the intrinsic capacity to perform automated optimization of a large range of chemical transformations and multistep syntheses. We selected six important and widely used reactions to exemplify this point: Buchwald-Hartwig amination, Horner-Wadsworth-Emmons olefination, reductive amination, Suzuki-Miyaura cross-coupling, nucleophilic aromatic substitution (S_NAr), and a visible light photoredox reaction. We also selected a two-step process that would inform us about the amenability of the system toward multistep reaction optimization, which is especially useful in cases wherein the product of the first reaction is of limited stability (for example, ketene generation followed by alkene cycloaddition).

For these investigations, we used a general four-step protocol (Fig. 1A) in each optimization: (i) design of the reaction sequence (selecting the reagents, solvents, and catalysts); (ii) attachment of the appropriate module to each bay and loading of the reagents and solvent feeds; (iii) selection of the parameter boundaries (time, temperature, catalyst loading) within which the system will perform the optimization; and (iv) execution of the automated optimization. We also found that remote operation and monitoring of the system during an optimization are possible with any smartphone, tablet, or computer that has internet access.

The Buchwald-Hartwig amination is central to many areas of chemical research, including the discovery and development of pharmaceuticals, agricultural chemicals, and organic light-emitting diodes (*32*). The palladium-catalyzed coupling of 1-bromo-4-methoxybenzene (**1**) with 4-methoxyaniline (**2**) under basic conditions was investigated using the recently reported (*33*) $BrettPhosPdG_3$ pre-catalyst (**3**). Figure 2A shows the platform setup for the reaction optimization. Bays 1 and 2 were used for reagent addition and mixing, and the amination itself was performed in bay *3* using a heated reactor. Introduction of toluene and water in bay 4 then enabled a continuous liquid-liquid separation in bay *5*. A 60-nl sample of the organic layer was analyzed directly by an in-line HPLC system, with the conversion of aniline **2** assayed relative to an internal standard. The complete results of the automated optimization sequence may be found in fig. S17 and tables S1 and S2. The desired secondary amine **7** was obtained in a 72% yield after the in-line purification. The reproducibility of the system that we observed also merits comment. The 72% yield obtained after the automated optimization of the Buchwald-Hartwig amination was replicated (72% yield) by another user operating the system under the same conditions, i.e., without reoptimization.

With the optimum conditions in hand, we next used the system to investigate the substrate scope under identical conditions (Fig. 2C), thereby providing the opportunity to study valuable structure-reactivity relationships in an exceptionally controlled manner. If desired, the user may also optimize each individual case using this automated system. The palladium-catalyzed coupling reactions of the anilines and arylbromides examined proceeded with overall chemical yields of 72 to 99% and with material throughput rates of 430 to 816 mg/hour.

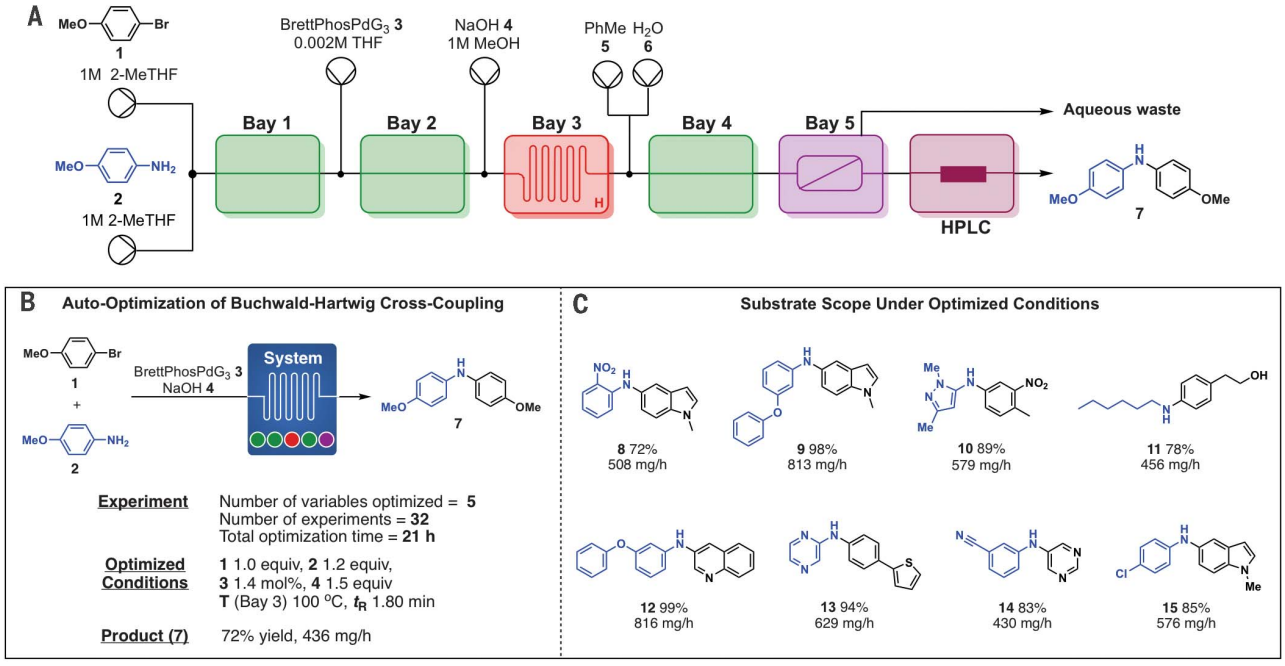

Fig. 2. Buchwald-Hartwig cross-coupling automated optimization and examples. (**A**) The system setup for the optimization of the Buchwald-Hartwig cross-coupling using a heated reactor in bay 3 and a liquid-liquid separator in bay 5. (**B**) Summary of the optimal conditions found for the Buchwald-Hartwig amination (details in fig. S17 and tables S1 and S2). (**C**) Substrate scope evaluated using optimized conditions determined in (B). Isolated yield after column chromatography. T, temperature; t_R, residence time.

Optimization of six additional reactions and sequences allowed us to test the generality of the system. Each of the following employed a unique array of modules in the five universal bays: Horner-Wadsworth-Emmons (HWE) olefination, reductive amination, Suzuki-Miyaura cross-coupling, S_NAr, the generation of an iminium electrophile via photoredox catalysis, and ketene generation with subsequent alkene cycloaddition (Figs. 3 and 4; complete details in supplementary materials). The HWE, for example, is a two-step process (phosphonium ylide generation and alkene formation), and optimization in the system used heated reactors in bays 1 and 2. As shown in Fig. 3B, after the automated optimization of the model reaction (32 reaction conditions examined in a continuous 10-hour period), a range of olefins were obtained under the same conditions in high yield with throughput up to 3.1 g/hour. Although the structures of the aldehyde, ketone, and phosphonate reagents were varied, all those examined underwent efficient HWE transformations under the optimized conditions.

In a similar manner, but with another system configuration, a two-step reductive amination sequence was optimized (33 experiments in 14 hours, Fig. 3C). The system discovered that a total residence time of 2.05 min was sufficient for the synthesis of amine **33**. The stereochemical integrity of chiral amines and aldehydes was preserved in the two cases that the system examined (**38** and **40**). The more hindered amine **36** provided a lower yield when subjected to the previously optimized reaction condition; incomplete imine formation (bay 1) followed by direct reduction of the aldehyde (bay 2) afforded appreciable amounts of an alcohol byproduct (details in supplementary materials). Nevertheless, highlighting another feature of the system, a rapid reoptimization of the imine formation step provided **36** in 97% yield. The Suzuki-Miyaura cross-coupling optimization (Fig. 3E) was performed using a packed-bed

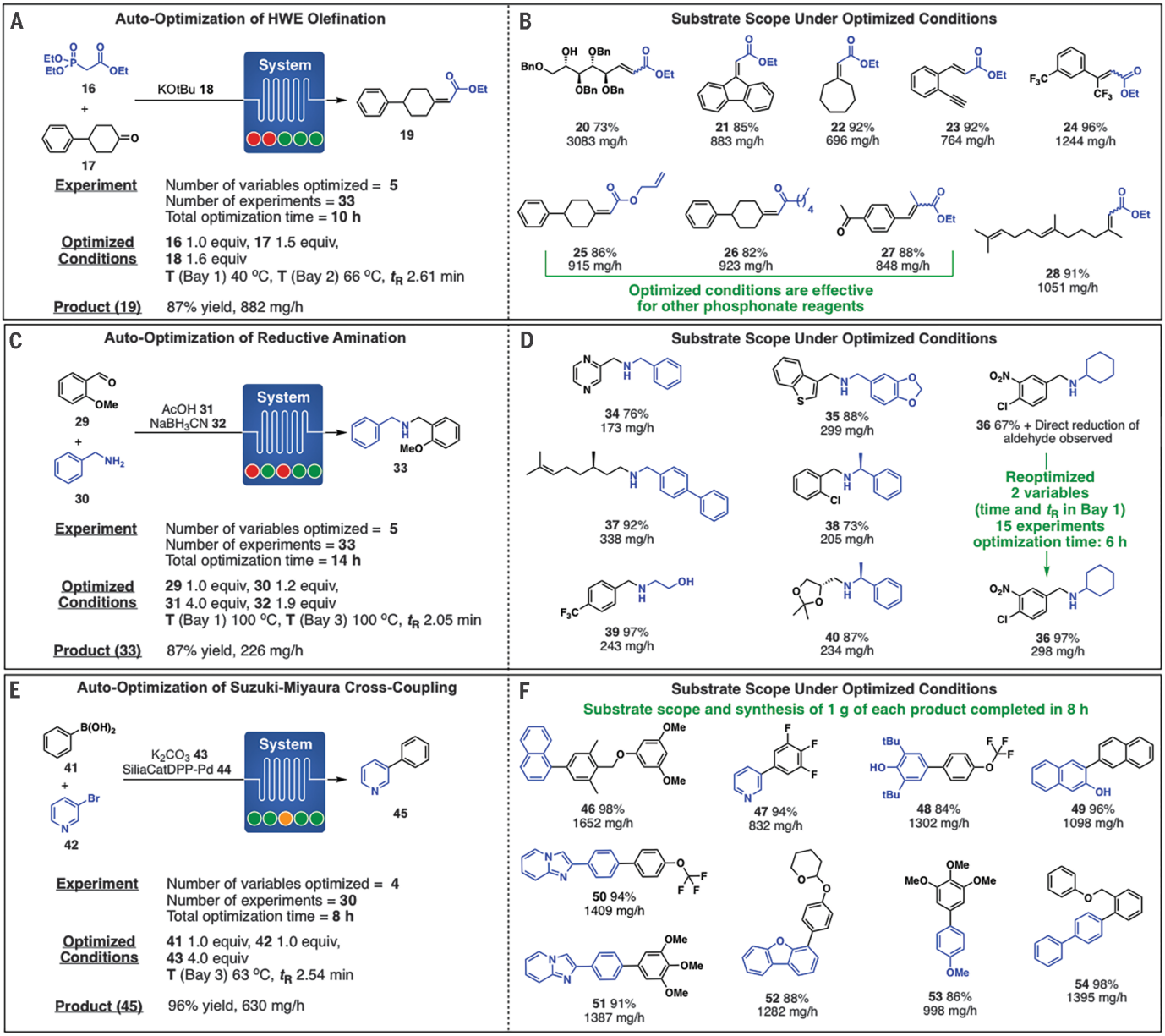

Fig. 3. Three different transformations optimized and demonstrated in the system. (**A**) HWE auto-optimization (details in fig. S17 and tables S1 and S3). (**B**) Substrate scope evaluation under optimized conditions in (A). (**C**) Reductive amination auto-optimization (details in fig. S18 and tables S1 and S4). (**D**) Substrate scope evaluation under optimized conditions in (C). (**E**) Suzuki-Miyaura cross-coupling auto-optimization (details in figs. S19 and S20 and tables S1 and S5). (**F**) Substrate scope evaluation under optimized conditions in (E). Isolated yield after column chromatography. T, temperature; t_R, residence time.

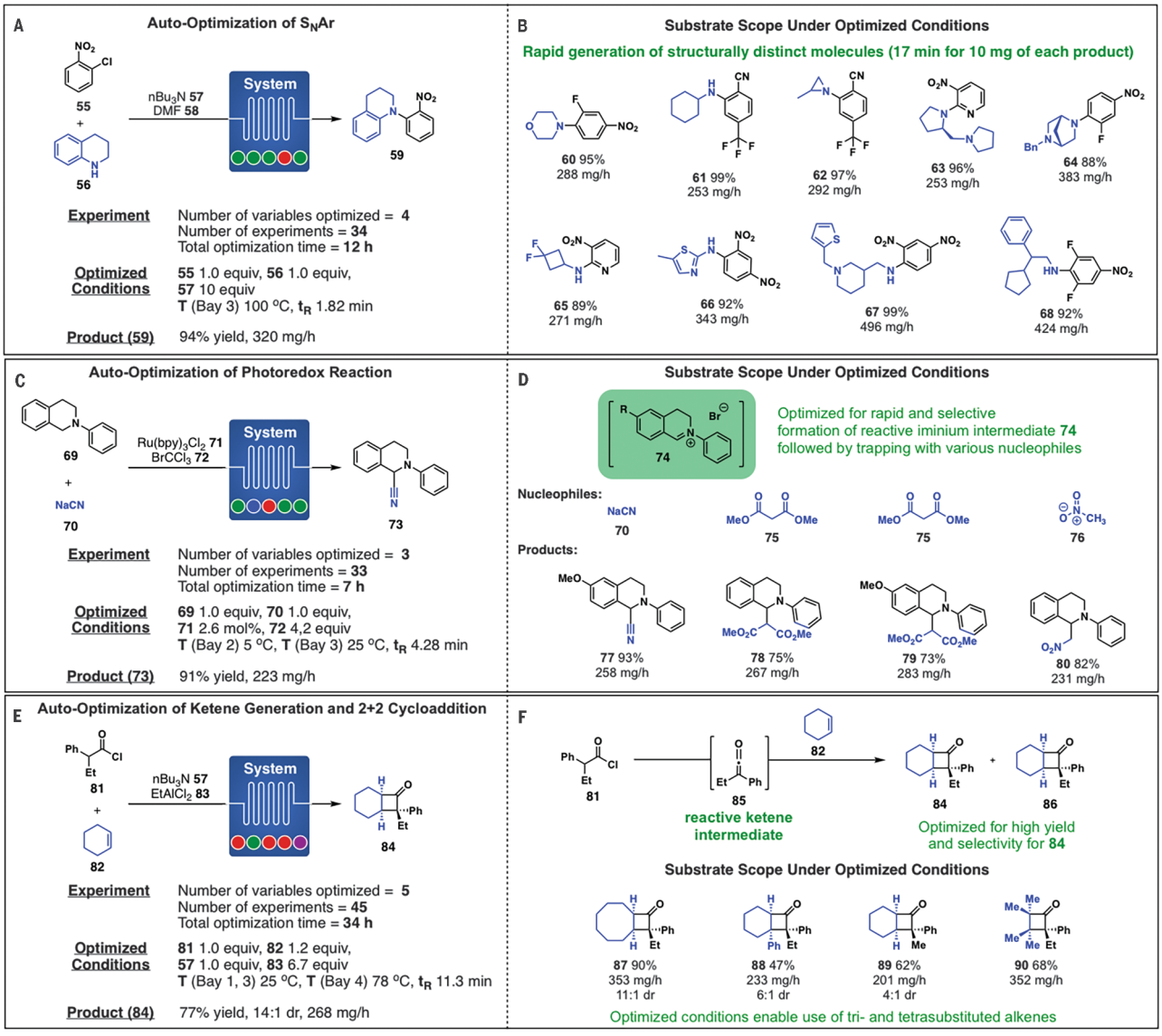

Fig. 4. Automated optimization of substitution and photochemical reactions using the platform. (**A**) Summary of the optimal conditions found for the S_NAr (details in fig. S21 and tables S1 and S6). (**B**) Substrate scope evaluated using optimized conditions established in (A). (**C**) Summary of the optimal conditions found for the photoredox reaction (details in figs. S22 and S23 and tables S1 and S7). (**D**) Substrate scope evaluated using optimized conditions determined in (C). Isolated yield after column chromatography. (**E**) Auto-optimization of ketene generation and [2 + 2] cycloaddition (details in fig. S24 and tables S1 and S8). (**F**) Multistep reaction sequence in (E) and substrate scope evaluation under optimized conditions in (E). Isolated yield after column chromatography. T, temperature; t_R, residence time.

reactor containing the solid-supported catalyst silia*Cat* DPP-Pd (*34*). Automated experimentation (30 experiments in 8 hours) provided conditions that afforded **45** in 96% yield and were transposed to a wide variety of other cross-coupling partners (Fig. 3F, **46** to **54**). Because the reagent feed can be exchanged rapidly, only 8 hours were required to provide 1 g of each of nine desired products, demonstrating the ability of the system to generate synthetically useful quantities of desired materials in a short period of time.

We next explored an S_NAr reaction. Automated optimization of the model reaction (Fig. 4A) required 12 hours and afforded tertiary amine **59** in 94% yield. Using the optimized conditions, we obtained several distinct structures (**60** to **68**) in high yields (88 to 99%). The rapid generation of a library of nine compounds (10 mg scale) was achieved in a total time of only 20 min, demonstrating the potential of this system for use in discovery efforts in, for example, the pharmaceutical industry. Furthermore, because the system operates at steady state using continuous-flow chemistry, scaling up of a reaction occurs readily and rapidly (*4*). For example, 10 mg of **59** was obtained in 5 min, corresponding to 7.7 g of amine **59** per day. The LED photoreactor, which includes active cooling for temperature control, was then applied to an automated optimization of a photoredox reaction (Fig. 4C) that proceeds by way of a reactive intermediate, iminium ion **74** (Fig. 4D). In this optimization, the boundary parameters were selected based on batch precedents from the Stephenson (*35*) and Rueping (*36*–*38*) groups. Under the optimized conditions, reactions were complete within 3 min, whereas previous reports indicate that a 3-hour reaction time was generally required in batch (*4*, *39*, *40*).

To investigate the ability of the system to optimize multistep sequences, we targeted a ketene generation and Lewis acid–promoted alkene cycloaddition to form cyclobutanones, inspired by a precedent from Brown (*41*). The first reaction produces the reactive ketene intermediate **85** from the acyl chloride **81**, and cycloaddition of

cyclohexene **82** affords cyclobutanone **84**. In-line quench and separation prior to analysis and product collection purifies the reaction mixtures. As the entire system may be operated under an inert atmosphere (N_2, for example), it provides a means for the safe handling of the pyrophoric Lewis acid ethylaluminum dichloride **83** by minimizing direct manipulation of this reagent by the user. Also noteworthy was that the objective function used in the optimization included terms for both product yield and selectivity for **84**, highlighting the flexibility of the optimization approach. The desired cyclobutanone **84** was produced in 77% yield and 14:1 diastereomeric ratio, comparable in both efficiency and selectivity to the Brown precedent, but at much higher temperature (78°C versus <23°C). This approach also expanded the scope of this valuable transformation; under the optimized conditions, cyclobutanones from tri- and tetrasubstituted alkenes, not possible in the originally reported conditions (*41*), may now be synthesized.

Outlook

In conclusion, we have developed a fully integrated, versatile system and demonstrated the automated optimization of a diverse array of chemical reactions. The examination of the substrate scope in each of the seven reactions and multistep sequences afforded greater than 50 compounds in high yield. This reconfigurable system has changed the way we approach experimentation and optimization in several ways. It accelerates the synthesis of lab-scale quantities of molecules and allows investigators to direct more of their efforts toward the creative aspects of research. The system's generality and ease of use obviates the need for expertise in flow chemistry to realize its benefits. The system also provides a means to optimize and evaluate the scope of a reaction in a matter of hours or days and do so under identical reaction conditions for each substrate of interest, if desired. Transfer of experimental results is now direct, electronic, and seamless; the time-consuming exercise of reoptimizing literature procedures should thus diminish in its frequency. Moreover, the data obtained in each optimization and evaluation may build a foundation of knowledge useful in machine learning pursuits.

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SUPPLEMENTARY MATERIALS

www.sciencemag.org/content/361/6408/1220/suppl/DC1
Materials and Methods
Figs. S1 to S81
Tables S1 to S8

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Reconfigurable system for automated optimization of diverse chemical reactions

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A self-optimizing reactor

Chemists spend a great deal of time tweaking the conditions of known reactions. Small changes to temperature and concentration can have a big influence over product yield. Bédard *et al.* present a flow-based reaction platform that carries out this laborious task automatically. By using feedback from integrated analytics, the system converges on optimal conditions that can then be applied with high precision afterward. A series of modules with heating, cooling, mixing, and photochemical capabilities could be configured for a broad range of reactions. These include homogeneous and heterogeneous palladium-catalyzed cross-coupling, reductive amination, and the generation of sensitive intermediates under an inert atmosphere.

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