Flow parallel synthesizer for multiplex synthesis of aryl diazonium libraries via efficient parameter screening

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The development of miniaturized flow platforms would enable efficient and selective synthesis of drug and lead molecules by rapidly exploring synthetic methodologies and screening for optimal conditions, progress in which could be transformative for the field. In spite of tremendous advances made in continuous flow technology, these reported flow platforms are not devised to conduct many different reactions simultaneously. Herein, we report a metal-based flow parallel synthesizer that enables multiplex synthesis of libraries of compounds and efficient screening of parameters. This miniaturized synthesizer, equipped with a unique built-in flow distributor and $n$ number of microreactors, can execute multiple types of reactions in parallel under diverse conditions, including photochemistry. Diazonium-based reactions are explored as a test case by distributing the reagent to 16 ($n = 16$) capillaries to which various building blocks are supplied for the chemistry library synthesis at the optimal conditions obtained by multiplex screening of 96 different reaction variables in reaction time, concentration, and product type. The proficiency of the flow parallel synthesizer is showcased by multiplex formation of various C–C, C–N, C–X, and C–S bonds, leading to optimization of 24 different aryl diazonium chemistries.

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Continuous-flow technology\(^1\)-\(^3\) for chemical synthesis offers better reproducibility, higher selectivity and better control over various reaction parameters than batch technology\(^4\)-\(^10\). The advent of the technology has led to the development of “universal” automated flow synthesis platform for efficient optimization of organic synthesis\(^11\),\(^12\), computer-aided synthesis planning (CASP) and robotically executed target-oriented or diversity-oriented flow synthesis of specific molecules for exploration of new drug development\(^13\)-\(^22\). In addition, on-demand synthesis of small molecules\(^23\), use of reconfigurable system\(^24\) and arrays of commercially available multiple reactor modules have elevated the flow capabilities to a new horizon, which are mostly focused on the synthesis of target molecules.

In general, to select a specific target molecule requires numerous screening synthesis tests and optimization. The traditional batch approach of “design–synthesis–screen” for the discovery of a lead molecule is time-consuming and/or at high risk with low probability of success\(^24\). Optimization and screening of variables for a chemical reaction is an issue that has troubled synthetic community throughout the history\(^25\). Currently, synthetic community mostly relies on commercially available batch synthesizers for quick screening of solvents, reaction temperatures, reagents and concentrations for high product yield and purity. These batch parallel synthesizers usually require simultaneous handling and integration of a large number of reaction flasks on a single platform. A screening approach based on microwell platform allowed a high throughput in identifying additive combinations for organic reactions\(^26\)-\(^31\). A recent elegant approach of handling reagents in nano-liter volumes using micro-liter plate system in batch mode enhanced the efficiency of optimization of an early phase of any natural product or drug discovery programme\(^32\). Formation of the “A × B” libraries in flow are mostly based on segmented flow system with highly enhanced mass and heat transfer, leading to screen catalysts\(^33\)-\(^35\), combinatorial chemistry\(^12\),\(^17\) and nanomaterials\(^36\). However, these approaches have limitations in direct utilization of the derived optimal reaction conditions into continuous-flow process.

On the other hand, in spite of the tremendous advances made for the continuous-flow technology for synthesizing a given target molecule, the reported flow platforms are mostly based on either linear or radial approach to perform single or multistage transformation in a sequential way, and they are not devised to conduct many different reactions simultaneously\(^22\). It is rather ironic that no significant progress has been made in utilizing continuous-flow synthesizer for the purpose of synthesis, screening and optimization, except a primitive 2 × 2 parallelized capillary system that enabled to conduct only several reactions\(^37\). From chemist’s perspective, it would be highly desirable to have a flow parallel synthesizer that enables synthesis combinations of \(A_i \times (B_1, B_2, B_3, ..., B_n)\) in a multiplex mode in one single action, instead of multiple \(A_i \times B_j\) type reactions sequentially as shown in Fig. 1. Here, we present a metal-based flow parallel synthesizer for synthetic screening and optimization. This flow parallel synthesizer has a damper-based distributor with baffles that enables uniform flow distribution and allows the system to operate without interruption when clogging occurs in some of the capillaries. Therefore, the synthesizer can concurrently execute multiple reactions in parallel under diverse reaction conditions, including photochemistry. This desk-top type of synthesis platform is utilized to explore diazonium-based reactions as a test case for multiplex screening of 96 different reaction variables in reaction time and concentration in building the chemistry library. The efficacy of the flow parallel synthesizer is demonstrated by enabling multiplex formation of various C–C, C–N, C–X and C–S bonds, leading to optimization of 24 different aryl diazonium chemistries, including a scaling-up test, simply by switching aryl diazonium salts. No reconfiguration of modules and components is involved in demonstrating the capabilities of this flow parallel synthesizer that can expedite the workflow in the discovery stage for a lead molecule.

**Results and discussion**

**Design principle of flow parallel synthesizer.** To date, parallel type of microreactors have been mainly concerned for the purpose of high-throughput production\(^38\)-\(^44\). In this work, the concept of parallelization is used to develop the new approach for the reaction screening and optimization of chemistry. The metal-based flow parallel synthesizer in Fig. 2 (Supplementary Fig. 1, see Supplementary Information for the details) is an assembly of multiple modules with specific functions. These modules are a flow distributor embedded with a baffle disc, two inlets at the bottom of the distributor, a set of independent individual outlets connected to the same number of mixers and a set of coiled capillaries of microreactors\(^45\).

One main design consideration was to ensure even flow distribution to the feed lines from the distributor in spite of

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**Fig. 1 Comparison of the reported approach and our parallel approach in flow system.** The reported approaches (left) in flow system mostly performs \(A_i \times B_j\) type reactions sequentially. On the other hand, our parallel approach (right) uses the flow parallel synthesizer to enable composite combinations of \(A_i \times (B_1, B_2, B_3, ..., B_n)\) in multiple modes in a single operation.
clogging or in the presence of separate side feeds. Another consideration was the potential to decouple the flow of the main species stream from the flows of the building block species. All the modules and components were modelled using a 3D CAD (Computer-Aided Design) program to arrive at the design shown in Fig. 2a. The baffle discs with complex structures in the distributor were fabricated by 3D metal printing, and the components and modules were made by computer numerical control (CNC) machining. The manufactured modules were assembled by connecting to stainless-steel capillaries and pumps using union-type, T-type and bending-type Swagelok connectors, rendering a complete setup of metal-based parallel flow synthesizer as shown in Fig. 2b.

Figure 3a shows a schematic of the flow parallel synthesizer of Fig. 2a. Typically, the main species is introduced through both or one of the two main inlets (D1 and D2) located at the bottom of the distributor, and cleaning liquid would be in-need introduced through the inlets. The distributor sends out equal amounts of the main species through \( n \) number of capillary feed lines, \( n \) being 16 in this case. Two coiled capillaries connected to both sides of T-mixer induce certain pressure drop as calculated in Supplementary Fig. 2, and it acts as a back pressure regulator to render the reliable flow distribution of main reagent at a few different flow rates of building blocks. The building blocks to react with the main species are introduced through 16 independent inlets (I1 through I16) to each individual T-mixer (T1 through T16) to be mixed with the main species. The mixed solutions proceed to individual capillary microreactors (R1 through R16) for 16 independent reactions. These coiled capillary reactors are equipped with heating units for independent temperature control, as revealed by the IR imaging at two different temperatures, 75 and 100 °C (Supplementary Fig. 3). Peristaltic pumps (P1–P3) are installed for individual residence time adjustment in three capillaries. R1 is a capillary reactor composed of transparent PFA tubing for photoreaction, and R2–R16 is composed of stainless-steel tubing.
To investigate the flow behaviour in the parallel synthesizer, computational fluid dynamics (CFD) analyses were conducted by utilizing the modelling results produced through the 3D CAD program (Supplementary Note 1, Supplementary Figs. 4, 6–8 and Supplementary Tables 1 and 2). The CFD results were also compared with the actual experimental flow rates (Supplementary Figs. 4–7 and Supplementary Tables 1 and 2). The uniformity of the flow distribution was quantified as a maldistribution factor (MF) that is a standard deviation of average mass flow rate at 16 capillaries. The numerical MF values at various flow rates are calculated to be less than 1%, while the experimental MF values measured by the collected amount of DMSO solvent as well as benzene diazonium tetrafluoroborate solution are less than 4% (Supplementary Figs. 4 and 5, Supplementary Table 1 and Supplementary Video 1). A low MF value corresponds to a more uniform flow distribution among capillaries.45

The reservoir-type distributor with a baffle-structure damper provides some unique features. For one, it maintains uniform flow behaviour at somewhat higher rates, even when clogging occurs in a single or several capillaries, in the rest of the capillaries. This feature contrasts the conventional flow reactor systems embedded with bifuarcation flow distributor that often causes a gradient flow profile along the remaining channels on clogging (Supplementary Fig. 6 and Supplementary Table 2).45,48 Another feature is that even when some of the capillaries are fed independently at different flow rates, uniform flow rates are maintained in the rest of the capillaries, which was confirmed both numerically and experimentally (Supplementary Fig. 7). These features allow multiplex synthesis under different conditions in reaction time and temperature. In addition, the dimensional effect of front coiled capillaries was thoroughly investigated by numerical analysis to compare decoupling of the main flow at all different flow rates of building blocks in the system (Supplementary Fig. 8). The longer and narrower coiled the capillary, the more clearly decouples the flow of the main species stream from the flow of the building block species.

**Flow parallel synthesis of aryl diazonium chemistry library and parameter screening.** Aryl diazonium forms a “transit hub” for arene chemistry from which almost any other aromatic derivative can be prepared, owes its chemical versatility to the −N2+X− functional group called “super electrophile” serving as a good leaving group. It is capable of reacting with any nucleophile such as hydrogen, oxygen, nitrogen, halogen, sulfur and carbon via ionic or radical pathways, to form almost any forms of bonds.49 Moreover, the way of diverse functionalization can be an important model case to screen for preparation of novel chemical entities or generation of diverse chemical libraries that can serve either as leads in drug discovery or starting materials for next reactions.49 Therefore, aryl diazonium-based reaction was chosen as a model for demonstrating a wide range of flow chemistries by performing efficient parameter screening and building synthesis library with the developed flow parallel synthesizer.

Initially, benzenediazonium tetrafluoroborate (a), one of the simplest and stable diazonium precursors, was used as the aryl diazonium salt to explore 6 aromatic substitution reactions, 1 azo-coupling reaction of a carbocycle at five different concentrations for the reasons elaborated shortly, and 5 azo-coupling reactions of heterocycles. All these 16 reactions took place simultaneously in the 16 microreactors, as shown in Fig. 4. After establishing optimal conditions, p-toluidiazonium tetrafluoroborate (b) as alternative aryl diazonium salt was additionally used to generate product libraries.

In the experiment with benzenediazonium tetrafluoroborate (a), 0.77 M solution of a in DMSO was pumped using an HPLC pump through the two main inlets (D1 and D2, Fig. 3) at six different flow rates ranging from 0.35 to 10.56 mL/min. This stream of diazonium solution was uniformly distributed into 16 individual stainless-steel capillaries of the flow synthesizer, the flow rate in the capillaries ranging from 0.022 to 0.66 mL/min, which corresponds to 1/16 of the total flow rate of the diazonium solution out of the distributor. The flow rate of the chemical building blocks entering the T-mixers was the same as that of diazonium stream.

The feed of chemical building block to the inlet I1 that enters the mixer M1 (refer to Fig. 3a) was a mixture of 7.7 M solution of furan and 5 mol% eosin Y (6) for a photochemical reaction. The feeds to the inlets I2 through I8 are: 0.77 M solution of CuCl (2) to I2, 0.77 M solution of KI (1) to I3, and 0.51 M solution of imidazopyridine (8, 9, 10) and imidazothiazole derivatives (11, 12) to I4–I8 for azo-coupling reactions of heterocycles. The feeds to the inlets I9 through I11 are: 0.77 M solution of NaN3 (3) to I9, 0.77 M solution of sodium salt of p-thiocresol (4) to I10 and
neat solution of furan containing 5 mol% of 4-aminomorpholine catalyst (5) to II1 to demonstrate aromatic substitution-based reactions. Mixtures of 0.64, 0.51, 0.38, 0.32 and 0.26 M of β-naphthol (7) and NaOH were fed to the inlets I12–I16, respectively, for concentration screening of the azo dye-based carbocycle. The 16 chemical building block feeds mixed with the diazonium solution went through diverse bond forming reactions simultaneously in 16 capillary microreactors via substitution and radical pathways in a multiplex mode.

In the parallel synthesizer, 16 samples out of 16 microreactors (R1–R16) can be taken for the yield determination for a given residence time or flow rate once the experimental setup including pumps and feed solutions are ready. Six different residence times of 30, 60, 120, 300, 600 and 900 s were chosen for an optimization. At the end of screening 6 different residence times by merely changing the flow rate, 16 × 6 = 96 samples in total were collected to find the optimal parameters in reaction time and concentration that produced the highest yields, as summarized in Supplementary Table 3 and graphically shown in Fig. 5.

The 96 screening data tabulated in Supplementary Table 3 reveal some interesting facts that deserve comments. Notable is the fact that the optimal residence time for all the reactions except for 3 aromatic substitution-based reactions can be taken as 60 s, when a few percent higher yield is ignored in favour of lower residence time or higher throughput. An example is the reaction in the reactor R6 for which the yield is 85% when the residence time is 60 s and it is 87% when the time is 120 s, for which 60 s was chosen as the optimum. These yields are comparable to those attained in batch reactors, some values being higher and some others lower than the batch yields. A sharp contrast in reaction time, however, is noted: 1 min for the continuous-flow reactor but 900 s, generating 6 × 5 = 30 concentration-based data points to arrive at an optimal concentration for good productivity. Clogging can be caused by precipitation of a poorly soluble product in DMSO solvents in azo-dye synthesis. As shown in Supplementary Table 3 and Supplementary Video 2, clogging occurred whatever the residence time is when the concentration was 0.51 M or higher. For lower concentrations of 0.26, 0.32 and 0.36 M, the clogging occurred only when the residence time was extended to 600 and 900 s. Long residence time or low flow rate often led to the deposition of dye product precipitates, causing the clogging. The optimal concentration chosen was 0.38 M for which the yield of Sudan dye was 74%. Whenever capillary clogging occurred, the total diazonium flow has to be reduced by 6.3% manually for each of the clogged capillaries and the corresponding building block flow halted. This procedure provided the same flow conditions for the rest of the capillaries and the reactions proceeded in the remaining reactors without interruption (Supplementary Fig. 6).

The total time required for screening 16 × 6 = 96 cases was approximately 60 min including the times needed to reach steady state for 6 different residence times, which is far less than the one performed in batch mode. The parallel synthesizer developed here...
is cost-effective, user friendly and highly efficient from screening point of view with minimum labour requirement.

Two different aryl diazonium salts, benzenediazonium tetrafluoroborate (a) and p-toluidiazonium tetrafluoroborate (b), were used to finally prove the multiplex synthesis of 24 compound libraries. The optimal conditions established for benzenediazonium tetrafluoroborate (a) were applied to p-toluidiazonium tetrafluoroborate (b) to generate 24 (12 × 2) product libraries in a time interval of 30 min, which included washing and stabilizing step to achieve steady state (Supplementary Video 3). The diazonium flow rates to R1, R2 and R3 were 0.033, 0.17 and 0.66 mL/min, respectively, and the flow rates to R4-R16 were the same at 0.33 mL/min, bringing the total diazonium flow rate to 5.14 mL/min. The yields for all the samples collected from their respective outlets of the parallel synthesizer were summarized in Fig. 6. In general, the synthetic yield of the flow parallel synthesizer was comparable to those of batch and single capillary reactors. From academic and industrial perspective, this flow parallel synthesizer could minimize time, labour and capital investment, enhancing hit-to-lead optimization success ratio especially for pharmaceuticals from lab to commercialization. This system can be developed further for autonomous sequential multiplex synthesis by introducing artificial intelligence (AI) planning technology in the future, with features of automatic blockage detection and flow adjustment.

Methods

General methods. All the reagents and solvents used were of commercial grade. All the reactions were carried out in a flow parallel synthesizer or single capillary reactor. Parts for the flow parallel synthesizer configuration were purchased from IDEX Health & Science LLC. The tube connecting the pump and platform consisted of high-purity PFA and PTFE tubes (1/16″ O.D., 0.75 mm I.D.) and polyether ether ketone 1/4″ I.D., 0.28 nuts. Swagelok tube fittings (SS-100-1-1, SS-600-1-2, SS-100-3 and SS-100-9) were purchased from Swagelok. Stainless-steel capillaries with 1/16″ O.D. and 0.75 mm I.D. were connected to the distributor body through the Swagelok connector. O-Rings (SM9-4D, heat resistant fluorine rubber, 8.5 pi O.D. and 1.5 mm thickness) were purchased from Misumi Korea. Reagents were

| Reactor number | R3 | R2 | R9 | R10 | R11, R1 | R12 ~ R16 | R4 ~ R6 | R7 ~ R8 |
|---------------|----|----|----|-----|---------|-----------|---------|--------|
| Building block| KI | CuCl | NaN3 | Sta | 5, neat M | 7, 0.38 M | 8, X = H, 0.51 M | 11, X = H, 0.51 M |
| Diazonium salts | 1, 0.77 M | 2, 0.77 M | 3, 0.77 M | 4, 0.77 M | 6, 7.7 M M | 8, X = H, 0.51 M | 11, X = H, 0.51 M |
| Sequence 1 | a. 0.77 M | a1. 30 s, 65% | a2. 120 s, 57% | a3. 60 s, 85% | a4. 60 s, 55% | a5, 60 s, 60% | a6 60 s, 60% | a7 60 s, 73% | a8, 60 s, 76% | a9, 60 s, 74% | a10, 60 s, 75% | a11, 60 s, 76% | a12, 60 s, 74% |
| Sequence 2 | b. 0.77 M | b1. 30 s, 69% | b2. 120 s, 66% | b3. 60 s, 81% | b4. 60 s, 64% | b5, 60 s, 62% | b6 61 s, 61% | b7 60 s, 78% | b8, 60 s, 77% | b9, 60 s, 73% | b10, 60 s, 73% | b11, 60 s, 76% | b12, 60 s, 71% |

Fig. 6 Summary for optimized reaction conditions and yields for 24 parallel reactions. All reactions were carried out at room temperature. The yield was calculated from isolated product. a 4-Aminomorpholine (5 mol%) was premixed with building block solution. b Eosin-Y (5 mol%) was premixed with building block solution. c 530 nm green LED was used. The red boxed region represents the synthesizes based on substitution of nucleophilic aromatics, the purple boxed region represents azo-coupling of carbocycles, and the green boxed region represents azo-coupling of heterocycles.
Solution preparation of diazonium salts and other building blocks

Diazonium solution. 100 mL, 0.77 M solution of respective diazonium salts (77 mmol) were prepared using DMSO.

- Building Block 1: 10 mL, 0.77 M solution of KI (7.7 mmol) were prepared using DMSO:H2O (9:1).
- Building Block 2: 10 mL, 0.77 M solution of CuCl (7.7 mmol) were prepared using DMSO:HOCl (3:2).
- Building Block 3: 10 mL, 0.77 M solution of NaN3 (7.7 mmol) were prepared using DMSO:HOCl (9:1).
- Building Block 4: 10 mL, 0.77 M solution of p-thiocresol and NaOH (7.7 mmol each) were prepared using DMSO:H2O (2:5:1).
- Building Block 5: 10 mL of neat furan solution containing 4-aminomorpholine (0.385 mmol, 5 mol%).
- Building Block 6: 10 mL, 7.7 M solution of furan (77 mmol) and eosin Y (0.05 M, 5 mol%) were prepared using DMSO.
- Building Block 7: 10 mL each of 0.6375, 0.51, 0.3825, 0.31875 and 0.255 M solution of β-naphthol and NaOH (1.9756, 5.1, 3.8523, 3.1875 and 2.55 mmol each) were prepared using DMSO:H2O (9:1).
- Building Block 8: 12–5 mL, 0.51 M solution of imidazopyridine/imidazothiazole (2.55 mmol) were prepared using DMSO.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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