A multicomponent reaction is established toward quinazolimine derivatives, but it requires intensive human interventions in conventional reaction systems to suppress the side reactions. Herein, an automated microfluidics-based reaction system that uses a program to command the fluid conductance to perform a cascade of reactions and separation in a defined sequence is innovated. The system is composed of chained reaction modules. Within the individual reaction module, side reactions are suppressed by creating an extremely high concentration bias between the reagents via selective reagent diffusion through the porous channel wall. The reaction sequence is commanded by transporting reagents from one module to the following ones, obtaining quinazolimine derivatives with high yield and purity. The system is low cost, easy to compose, program commanded, and requires minimal human intervention once the reaction modules are assembled and reagents are loaded.

1. Introduction

Multicomponent reactions are extensively used in synthesizing small molecule drugs,[1,2] drug precursors,[3–6] natural molecule derivatives,[7] and novel optoelectronic materials.[8–10] Side reactions are commonly seen in chemical synthesis. The current methods to improve chemoselectivity include using benzoquinone ligands,[11] solvent-controlled reaction,[12] screened metal catalysts,[13] and stepwise reactions that create concentration bias among the reactive substrates on purpose.[14,15] Improving the chemoselectivity for target products at reduced labor cost and system complexity remains a challenge. With the continuous reduction in the cost of machines as the industrial revolution, automation has been in pursuit to reduce labor costs, increase production efficiency, and free humans from repetitive and risky operations.[16,17] Recently, the marriage of chemical reactions with machine learning algorithms endows the reaction systems with intelligence in selecting on-demand reactions, searching for new reactivity, and optimizing reaction conditions.[18–20] But for many multicomponent reactions, the side reactions share a similar mechanism as the target reactions, which largely fail the aforementioned strategies to improve the yields and selectivity of target products.[21] Therefore, novel strategies must be implemented to promise reduced human intervention for multicomponent reactions with a high yield of target products and reduced byproducts.

Microfluidics was emerged over 50 years ago, which appeared first in electrophoresis for analyzing trace amounts of chemicals,[22,23] due to its ability to minimize the analyte units to incredibly small volumes. Microfluidics has also been used to detect DNA,[24,25] pH-sensitive reactions,[26] protein crystallization,[27] and various organic synthesis, including simple oxidant reactions[28,29] synthesizing benzaldehydes using phenyl methanol as the substrate, and cyclization reactions.[30–33] Microfluidics has developed into a wide-spectrum technology to manipulate fluids, but its capacity to conduct selective chemical reactions in automated manners remains to be explored.

Quinazolimine can be utilized as inhibitors of cholinesterase[14] and cMETkinase,[35] modulate activities of chemokine CCR3,[16] and exhibit cardiotonic and antiproliferative effects.[37,38] The synthesis of quinazolimine derivatives involves multicomponent reactions and requires a system with high reaction selectivity to proceed to on-demand reactions.[21] Herein, we design a diffusive microfluidics system with automation, in which a multicomponent reaction for synthesizing quinazolimine derivatives is proceeded with defined orders and suppressed side reactions, by offering the concentration bias via diffusive transport of one substrate in each step and subsequent reactions occurrence according to a coded command program.

2. Results and Discussion

2.1. Mechanism of the Reaction System

Automation of the reaction system is endowed by a programmed command that controls the flow conductance driven by syringe pumps. The chemoselectivity is contributed by the diffusive
transport of one reactive substrate into the volume of another substrate through a nanoporous membrane. Due to the significant size difference between the two substrates, the diffusive transport of the two substrates through the membrane is vastly different, which deliberately creates an extreme concentration bias between the two substrates. Both characteristics are highly controllable and tailorabile. Prior to initiating the passive transport of substrates via diffusion, the catalyst is placed in the volume that houses the more concentrated substrate demanded by the target reaction. In this case, the target reaction occurs with high selectivity and suppressed side reactions by the purposely created concentration bias.

While studying the multicomponent reaction of iodonium salts a, nitrile b, and 2-aminobenzonitrile c, we found four different products, including 2,3-diphenylquinazolin-4(3H)-imine A, 2,4-diphenylquinazoline B, 2-(4-imino-3-phenyl-3,4-dihydroquinazolin-2-yl)aniline C, and N-phenylacridin-9-amine D via the cascade reactions (Figure 1a). To further study the multicomponent reaction, we proposed the mechanisms for the four different products in Figure S1–S3, Supporting Information. According to the proposed mechanisms, 1 equiv. substrate a could react with 1 equiv. b and c to generate the target product A. Under the same reaction condition and catalyzed by Cu(OAc)₂ in toluene, 1 equiv. a could react with 2 equiv. b or c to generate the byproduct B or C, respectively. Alternatively, 2 equiv. a could react with 1 equiv. c and generate byproduct D (Figure 1a). Therefore, chemoselectivity becomes rather low.

We initiated our study on the multicomponent reaction first in the bulk system and screened the catalyst, solvent, and temperature conditions (Table S1, Supporting Information). It turned out that the yield of the target product in the screened conditions remained unimproved. Creating concentration biases among reactive substrates for each reaction might enable high selectivity. The conventional approaches, such as a multipot reaction and dropwise addition of substrates, are not only labor-intensive but ineffective in improving the yields. For example, we used a two-pot reaction system to conduct the synthesis of the intermediate 1 and the quinazolinimine derivatives, which were transferred to the subsequent modules by flow, controlled by syringe pumps, to accomplish the cyclization of the intermediate 1 and the substrate c for the target product A. The products, including A, C, and D, were then conducted to the chromatography column made in-house and filled with silica gel microbeads (particle size 10 – 40 μm) (Figure 2). The final products were separated, and the target product was collected in the customized column chromatography without any post-treatment. The reaction required almost zero human intervention because once the reaction was initiated after the substrates had been loaded and the modules been assembled, the programmed command took over the control till the products were separated and collected.

### 2.2. Illustration of the Reaction System

Herein, we designed a diffusive microfluidics system to access high chemoselectivity with minimal human intervention on introducing substrates. As shown in Figure 2, a three-component reaction was designed to occur in a reaction system containing two microfluidics modules for the cascade reaction, and a separation module (a housemade chromatography column) immediately following the two reaction modules. The reaction modules were composed of coaxially aligned tubes. A Teflon tube (the inner diameter [ID] 5 mm and the outer diameter [OD] 7 mm) was used as the outer channel; a gas chromatography column (SE-54, ID = 0.5 μm, OD = 0.5 mm) tube used as the inner channel. The wall of the inner channel allowed diffusive transport of the substrates, which was negatively correlated with the molecule sizes.

The three modules were connected by controlled flow conductance, automated by the syringe pumps accepting commands to drive fluid motion from the program. The modules were connected by Teflon tubes (ID = 5 mm, OD = 7 mm) to transport the reagents. The first module synthesized the intermediate 1 and the quinazolinimine derivatives, which were transferred to the subsequent modules by flow, controlled by syringe pumps, to accomplish the cyclization of the intermediate 1 and the substrate c for the target product A. The products, including A, C, and D, were then conducted to the chromatography column made in-house and filled with silica gel microbeads (particle size 10 – 40 μm) (Figure 2). The final products were separated, and the target product was collected in the customized column chromatography without any post-treatment. The reaction required almost zero human intervention because once the reaction was initiated after the substrates had been loaded and the modules been assembled, the programmed command took over the control till the products were separated and collected.

### 2.3. Passive Diffusion Creates Concentration Bias between the Reagents

The diffusion rate of the substrate b through the inner channel wall was characterized over 30 min and quantified by their absorption level in toluene out of the housing tube. The characterization was conducted under the ambient condition. As the substrate was moisture sensitive, its diffusion through the porous membrane over the course of 30 min was accompanied by its hydrolysis. The graph in Figure 3 shows the concentration of the substrate b in the outer channel reached by diffusion, represented by the absorption at the retention time of 4.3 min. As the absorption had been growing from the 20 min-curve to the 30 min-curve, it suggested the diffusion could sustain for over 30 min. The large peak at the retention time of 6.4 min implied that the substrate b hydrolyzed remarkably over the duration of diffusion evaluation. It is reasonable to infer that the fraction of hydrolyzed b would be smaller in the reaction module, as the b molecules were gradually consumed by the first and second reactions in the first two
modules (Figure 1a and Figure S1–S3, Supporting Information). The factor that the diffusion of $b$ was prolonged to over 30 min validated that the concentration bias of $a$ over $b$ was created in the diffusive microfluidics, generating the target product $A$ and suppressing the occurrence toward the byproduct $B$.

2.4. Sketch of the Stepwise Reactions

The first step was dedicated to synthesizing the intermediate 1, followed with the synthesis of the target product $A$. Reagents $a$ and $b$ were reacted first to generate the intermediate 1. To avoid
generating the byproduct B, by reacting 1 equiv. a with 2 equiv. b, the two reagents were controlled with extremely high concentration ratios of a over b in the first reaction module. This microfluidics module allowed nitrile (the substrate b) to diffuse gradually through the channel wall from the inner channel to the outer channel that housed iodonium (the substrate a) and compensate its consumption there (Figure 4a). Cyclization of the intermediate 1 with the substrate c could generate three intermediates (3, 2, and 4) and lead to three different cyclic compounds (A, C, and D) (Figure 5). When reacted in the second microfluidics module, the side reactions toward C and D were suppressed by introducing the concentration biases of the intermediate 1 over the substrate c, via diffusive addition of c to the reaction channel (Figure 4b).

Figure 2. The schematic diagram of the automated microfluidics system. a) The abstract of the organic synthesis. b) The diagram of the diffusive microfluidics system consisting of two reaction modules and one separation module. c) The chemical structures of the target products synthesized in the diffusive microfluidics system.

Figure 3. The diffusion characterization of the substrate (benzonitrile) through the inner channel. The substrate was dissolved in toluene in the inner channel (a gas chromatography column [SE-54, ID = 0.5 μm, OD = 0.5 mm] tube) placed in a round flask, heated at 100 °C. The diffusive amount in the round flask was characterized in HPLC and quantified by their absorption magnitude. The three peaks represent (I) the substrate, (II, III) the hydrolyzed byproducts of the substrate.

Figure 4. Mechanism of the diffusive microfluidics module for the selective reaction. a) Sketch of the first step of reaction in the multicomponent reaction. b) Sketch of the second step of the reaction.

2.5. Outcome of the Reaction Improvement

Three different quinazoline derivatives were synthesized with good yield (77%, 81%, and 72%) in this automated microfluidics system (Table 1). Compared with the yields shown in Table S1, Supporting Information, the yields were dramatically improved in our automated microfluidics reaction system than the conventional one-pot reactions. The purity was also
significantly improved (Figure S4, Supporting Information). The structures of the three components were identified by $^1$H NMR and $^{13}$C NMR with high purity (Figure S5–S10, Supporting Information).

3. Conclusions

In conclusion, we have developed an automated microfluidic system for synthesizing a new series of quinazolimine derivatives. The chemoselectivity was contributed by the diffusive transport of substrates that generated concentration biases to direct the reaction pathway. The system was automated and allowed minimal human intervention once the substrates were loaded in syringes and conducted by the programmed computer command. This automated system may offer a new approach for a wide range of multicomponent reactions with high chemoselectivity, yield, and purity, and extremely low labor force requirements.

The establishment of automated reaction systems applicable to multicomponents reactions has significant promises in both pharmaceutical and chemical engineering industries. The system could be scaled up using multichannel tube arrays ended with multi-to-one tube connectors as the inner tubes, as shown in Figure S11, Supporting Information. In this design, the diffusive dynamic is not altered, but the diffusive area and reaction volume grow proportionally with the channel numbers.

The manufacturing cost of the diffusive tubes would be reduced to affordable ranges with the increase in popularity of this system. It reduces the demand for human intervention and thus free humans from repetitive and dangerous operations. The system can also be translated for other reactions with modification on the modules. Challenges may include the selection of materials to manufacture the diffusive tubes with tailored porosity for different substrates, but a wide choice of ceramic and polymer (e.g., silicone) membranes might provide solutions. Further improvement in both automation and efficiency is expected in the future with industrial standards of reaction tubes and separation modules, such as advanced chromatography, become in use.

4. Experimental Section

Materials: Benzonitrile, 4-chlorobenzonitrile, 2-aminobenzonitrile, 2-amino-4-methylbenzonitrile, iodobenzene, 1-bromo-2-iodobenzene, and copper (II) trifluoromethanesulfonate were purchased from TCI Chemical Co. Silica gel (particle size 10–40 μm) was purchased from Ocean Chemical Factory, Qingdao, China. Organic solvents (such as dichloroethane [DCE] and toluene) were used without distillation. All of the other chemicals were supplied by Aladdin Chemical Co. (Shanghai, China) and used without further purification unless mentioned otherwise.

Instrumentation: $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker AL-400 MHz spectrometer at ambient temperature with CDCl$_3$ as the solvent. Coupling constants (J) were given in hertz (Hz). The terms m, dq, q, t, d, and s referred to multiplet, doublet quartet, quartet, triplet, doublet, and singlet, respectively. Reactors were injected by LSP01-1A from LongerPump Co., China.

Synthesis of Diaryliodonium Salt: Substrate Ph$_2$IPF$_6$ was purchased from Alfa-Aesar. Substituted diaryliodonium salts derivatives except Ph$_2$IPF$_6$ were prepared according to the literature.[39,40] Synthesis of Quinazolimine Derivatives: The substrates, copper(II) trifluoromethanesulfonate and toluene were added to the outer channel, whereas the benzonitrile derivatives were added to the inner channel. The tube was heated to 100 °C for 1 h. Then the reaction mixture was transferred to the second microfluidics module by syringe pump-driven flow. 2-Aminobenzonitrile was added to the inner channel, and the reactor was heated at 100 °C for 4 h. After the reaction, the reaction mixture was transported to the separation module to be purified on silica gel (petroleum ether/ethyl acetate: 6/1).

![Diagram](image-url)

Figure 5. Cyclization of the intermediate 1 and the substrate c to generate the products A, C, and D.

Table 1. The yields of the target products.

| Weight [mg] | Molecular weight | Yield [%] |
|------------|------------------|-----------|
| 229        | 297.1            | 77.08     |
| 316        | 389.0            | 81.23     |
| 296        | 409.0            | 72.37     |

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Supporting Information
Supporting Information is available from the Wiley Online Library or from the author.

Acknowledgements
X.P. and H.Z. contributed equally to this work. This work was supported by the National Natural Science Foundation of China (grant no. 61971255), the scientific research start-up fund of Tsinghua-Berkeley Shenzhen Institute, the fund from the Shenzhen Science and Technology Innovation Committee (grant no. KQJSCX20180327143623167), and the fund from Shenzhen Development and Reform Commission Subject Construction Project [2017]1434.

Conflict of Interest
The authors declare no conflict of interest.

Keywords
automations, chemoselectivities, microfluidics, multicomponent reactions

Received: December 31, 2019
Revised: February 15, 2020
Published online: March 3, 2020

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