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Femtosecond laser-engineered 3D microfluidic chips: Synthesis system sprouting highly efficient multiphase organic reactions

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ABSTRACT

Recent developments in the utilization of microfluidic chips (MFCs) have shown their potential utility in multiphase organic synthesis by enabling efficient organic reactions in flow chemistry. However, MFCs technology has been wandering in the laboratory of small dose synthetic routes, which is limited to the level of "tiny" fluid flux. To address this issue, we herein report the first case of the chips with high-throughput 3D channels produced by femtosecond laser being used to create a time-saving, cost-effective and risk-free approach suitable for large-scale flow synthesis. Several multiphase reactions have been successfully prepared on demand in our designed flow synthesis system containing 3D MFCs: 1) benzyl alcohol was converted to benzaldehyde in 3 min with a yield of 97.50% by liquid-liquid two-phase transfer catalytic oxidation; 2) organozinc reagents and α-cyano carbonyl carbon compounds were synthesized by solid-liquid two-phase metal insertion reaction in 7 min, and the yield was up to 100%; 3) benzoic acid was synthesized by gas-liquid two-phase carboxylation reaction in 2.8 s with a yield of 96%. Significant gains in production rate result from the effective scaling of flow reactors from microliters per hour in MFCs to intermediate milliliters per minute without affecting mass transport performance. Meanwhile, our 3D MFCs show excellent mass and heat transfer efficiency in large-scale industrial units, breaking through the bottleneck in this field. As a result, it is possible to imagine the creation of a new, streamlined flow synthetic technique *via* MFCs for green multiphase organic synthesis.

Research using microfluidic chips (MFCs) has long been a popular topic in the realm of analytical chemistry [1–3]. Although most studies utilize the analytical potential of the MFCs, considerable attempts have also been made to endow microsystem technology for preparative applications as the research in organic chemistry continues [4,5]. Positive hopes for MFCs' synthetic applications are justified by enhanced heat and mass transmission in small-scale channels [6]. And numerous instances highlight the advantages of MFCs, such as the reduction in reaction time, saving reaction raw materials, precise parameters and greater conversion rates and selectivity, which can realize the rapid screening of reaction conditions and fit the concept of green chemistry [7,8]. Furthermore, because of the system's downsizing and the low cost of mass-producing MFCs, high-density continuous flow microsystem obviating unnecessary purifications and isolation are becoming more financially practical [9–11].

The possibilities and limitations of MFCs are dictated by both the material properties and fabrication techniques [12]. Most MFCs materials, such as PMMA and PDMS, have not yet been tried for wide areas of channels, and their chemical applications are restricted because of their poor tolerance for numerous organic chemicals and low chemical resistance [13]. Borosilicate glass is superior since it is more affordable, by contrast, has excellent chemical stability towards organic solvents, and strong acids and bases [14]. Due to processing limitations, high-throughput glass MFCs utilized in large-scale chemical manufacturing still stay in the 2D flow channel [15]. Some complex 2D chips include squeezing and contracting structures to enable fast mixing, nevertheless, this design results in a considerable pressure drop and the chip that is easily fractured. In addition to being easily blocked by synthetic chemicals, the chip also requires extra and large driving force, which is a waste of energy [16]. Meanwhile, the manufacturing procedures employed for 2D chips are unable to create sophisticated 3D channels that can permit more effective mixing [17,18]. In order to build 3D MFCs in the industry without stacking and gluing, femtosecond laser technology, which can perform high-

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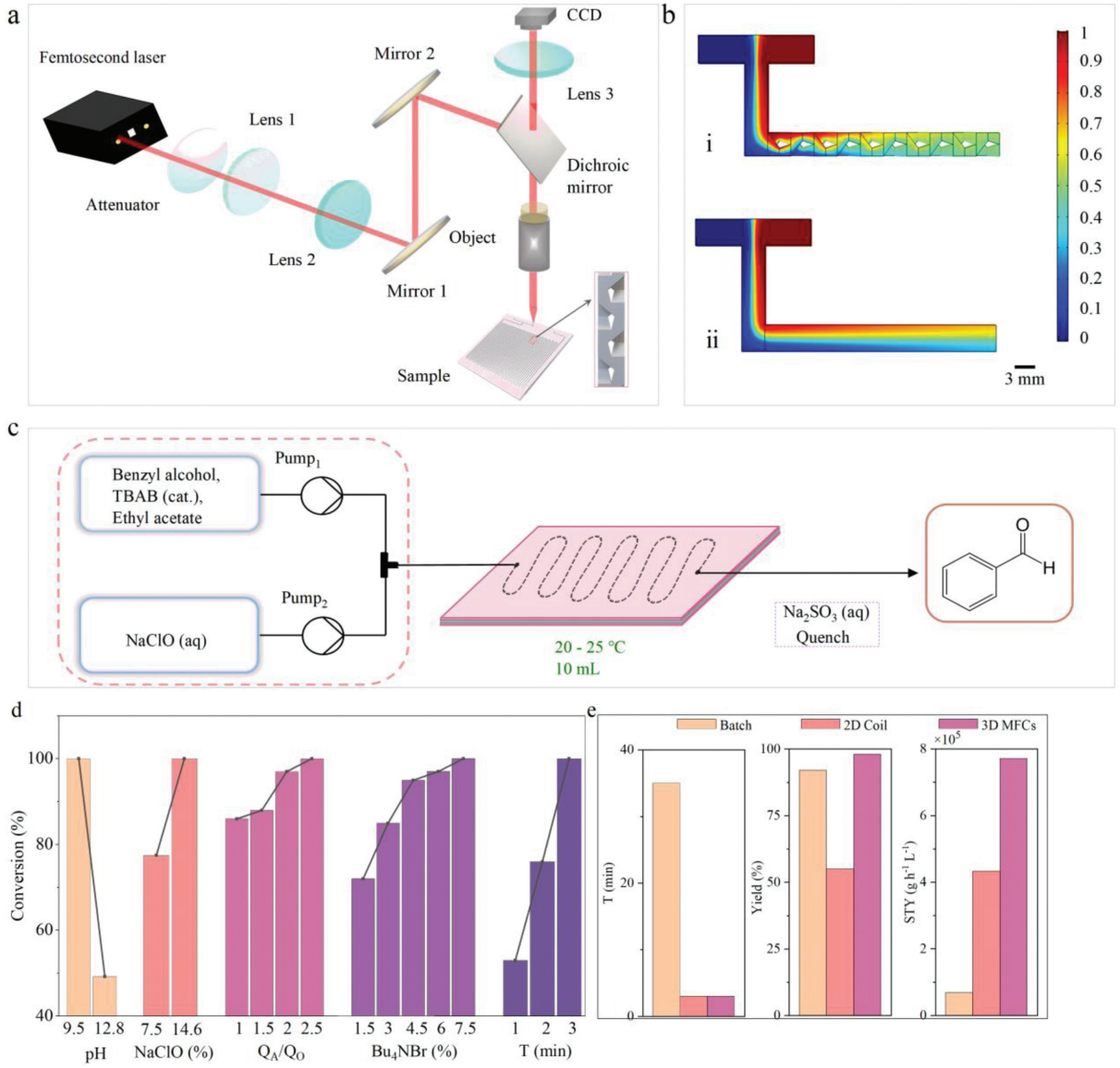


Fig. 1. (a) Diagram showing the experimental configuration for a 3D femtosecond laser machining system. Numerical simulations of mixing results in (b) (i) 3D and (ii) 2D microfluidic chips ($v = 0.3$ mL/min). The T-shaped intake section size of the channel was 3 mm × 4 mm. Fluids with molar concentrations of 1 mol/L and 0 mol/L were characterized by the colors red and blue, respectively. When two solutions were entirely mixed and their concentrations were close to 0.5 mol/L, they appeared green. (c) Processing continuous flow MFCs devices of liquid-liquid two- phase transfer catalytic oxidation reaction of benzyl alcohol to benzaldehyde. (d) The effect of the parameters: pH of the aqueous phase, the influence of different concentration of sodium hypochlorite solution, the ratio of Q_A and Q_O, the concentration of the phase transfer catalysts, the specific values were shown in Table S1 (Supporting information). (e) The Comparison between the batch, coil, and 3D MFCs process, the specific values were shown in Table S2 (Supporting information).

precision spatially-selective modification inside the glass, is given [19]. It also has been revealed, that the 3D channels created using Baker's transformation idea is capable of enabling quick and effective mixing even under low Reynolds number conditions [20,21]. For these reasons, we report an approach towards the high performance and low cost of micro reaction system *via* femtosecond laser-tailored 3D MFCs using Baker's transformation (Fig. S1 in Supporting information), able to realize the safe, efficient and clean multiphase reaction for large-scale chemical applications.

The method utilized in our MFCs fabrication may make an optically transparent material strongly absorb light by nonlinear absorption (multi-photon absorption), and then change the material's spatial resolution at the nanoscale processing scale (Fig. 1a). Then wet chemical etching makes it possible to fully implement 3D structure micromachining using a direct, mask-free method. The spatial and temporal distributions of molar concentrations in a 3D and 2D structures ($v = 0.3$ mL/min) are simulated using computational fluid dynamics (CFD) (Fig. 1b). And the mixing effect of the 3D channels was showed by using both blue and yellow ink (Fig. S2 in Supporting information). It has been demonstrated that our 3D structure has excellent mixing capabilities insensitive to Reynolds number, enabling the high efficiency mixing in extremely thin channels or throughout a wide range of flow speeds. This is the first report, to the best of our knowledge, where 3D channels with high density and large volume have been fabricated using femtosecond laser micromachining in borosilicate glass. The excellent mixing effect of the microchannel gives the multiphase reaction an excellent synthesis effect, which breaks the confinement of numerous phases, as this increases the mass transfer and response rates between the phases and provides strong control over mixing within each phase. Herein, the ability of this approach is demonstrated by performing optimizations and multistep synthe-

ses of targets, using liquid-liquid two- phase transfer catalytic oxidation reaction of benzyl alcohol to benzaldehyde, exploring solid-liquid two-phase metal insertion reactions for the preparation of organozinc reagents and α-cyano carbonyl carbon compounds, synthesizing benzoic acid by gas-liquid two-phase carboxylation reaction.

Liquid-liquid two-phase reaction: Benzaldehyde is extensively capitalized as intermediates while synthesizing pharmaceutical and agrochemical materials, and also participates in reactions such as condensation of hydroxylaldehydes, chlorination, nitrification, nucleophilic addition [22]. In particular, the phase-transfer catalytic reaction of the benzyl alcohol oxidation method to benzaldehyde, a typical liquid-liquid two-phase catalytic reaction, has been studied using continuous flow chemical technologies recently [23]. Inspired by the previous report which provided an oxidation method utilizing NaClO as oxidant and PFA coil as a reactor [24], we proposed the liquid-liquid heterogeneous reaction of benzyl alcohol to benzaldehyde in a 3D MFCs continuous flow device, using Bu_4NBr as catalyst and NaClO as oxidant. An essential basic organic chemical raw material, benzaldehyde, was successfully synthesized with a high yield (98%) when the residence duration was 3 min.

Optimization of benzyl alcohol oxidation was performed in the liquid-liquid two-phase reaction device shown in Fig. 1c. Benzyl alcohol (4.3252 g) and Bu_4NBr (0.9671 g, 7.5% equiv.) were dissolved in 50 mL ethyl acetate to prepare benzyl alcohol solution with a concentration of 0.8 mol/L. Then the $NaHCO_3$ was used to adjust the pH of the aqueous sodium hypochlorite solution. Finally, the stainless-steel needle at the joint of the inlet pipe of the two pumps was immersed in the aqueous phase and organic phase respectively. The regents were consistently added into the system by the HPLC pumps. The reactants were mixed in our lab-made 3D MFCs at a certain flow rate. The one-way valve could prevent the backflow of the reaction mixture, and BPR was used to maintain the pressure of the whole reaction system. The outflow liquid was quenched with Na_2SO_3 and analyzed by gas chromatography.

In order to prove the performance of the 3D MFCs, our primary objective was to discover a way to continue reducing the minimum residence time currently developed in flow chemistry (35 min) [24]. Initial experiments revealed that adjusting the pH of the aqueous phase to 9.5 was the most efficient technique to speed up the reaction out of all the other reaction parameters (Fig. 1d). The majority of the hypochlorite anions protonated at this pH, forming hypochlorous acid, which the phase-transfer catalyst subsequently extracted to the organic phase with the hypochlorite anion, greatly speeding up the process. Higher ionic strength in the saturated bleach made it easier to remove organic salts from the aqueous phase and introduce them into the organic phase. With the optimized pH levels, the influence of different concentrations of sodium hypochlorite solution on the reaction was investigated (Fig. 1d). When the sodium hypochlorite aqueous solution with 14.6% was used instead of 7.5%, the conversion rate of benzyl alcohol was increased by 100%, which indicated that the higher the available chlorine concentration of sodium hypochlorite, the stronger the oxidation. After the prior many influencing elements had been improved, it was thought to alter the water-organic phase interface area by varying the ratio of Q_A and Q_O to investigate the reaction (Fig. 1d). It could be seen that at Q_A:$Q_O = 1$, sodium hypochlorite aquatic solution had been excessively excessive, and when the ratio was gradually increased, the interface area of the water phase and the organic phase was also increased, and the conversion rate would increase to complete conversion. Five experiments were showed by varying the concentration of the phase transfer catalysts, and the conversion changes in MFCs were examined (Fig. 1d). The consequences displayed that an excellent conversion was found while 7.5% of Bu_4NBr were used. Further optimization was focused on the residence time (Fig. 1d). It was found that the excessive residence time would sacrifice mass transfer effect, which would reduce the yield. So, the total rate was greater than 5.5 mL/min, that is, when the residence time was greater than 3 min, the reaction could be completely transformed and the yield was obtained (Fig. S3 in Supporting information).

To reflect the strength of the 3D MFCs, the comparison with the process in coil and batch was shown in Fig. 1e (same reaction temperature, flow rate, concentration, pH). The reaction time was decreased by 10 times. Particularly, MFCs had a space-time yield that was 113 times more than that of a batch process. This proved that the continuous flow reaction device with 3D MFCs as the core could not only accurately control the reaction temperature, avoid the response out of control, but also reduced the length of the diffusion path. As a result, benzaldehyde was prepared for continuous, safe, efficient, and stable.

Solid-liquid two-phase reaction: On the basis of the previous experiment, we integrated the packed-bed reactor to build a continuous flow device of the solid-liquid. Using this device, we successfully prepared the α-cyano carbonyl compounds under flow conditions and optimized the reaction conditions. The α-cyano carbonyl compounds were often used to build bioactive molecules and played a unique role in the metabolic stability of the drug [25]. But the synthesis of α-cyano carbonyl compounds with all-carbon quaternary centers suffered from several drawbacks such as confined functional-group tolerance and harsh temperature and pressure conditions, especially when noble metal catalysts that were sensitive to air/moisture were used [26]. Zinc dust treatment of tertiary alkyl halides and electrophilic cyanation reagents led to the production of α-cyano carbonyl compounds without the use of metals [27]. Nevertheless, in the mass manufacture of organozinc reagent, it was typically required to add reagents gradually in order to eliminate the risk of excessive exothermic heat. At the same time, the activated organozinc reagent was air-sensitive, combustible, and difficult to store, following treatment of zinc is time-consuming and wasteful. These inspired us to explore the potential application of our flow device to exhibit both impressive robustness and remarkable flexibility in synthesis of α-cyano carbonyl compounds. The best reaction conditions in 3D MFCs, as compared to conventional synthesis, were as follows: reaction time of 7.1 min, temperature of 60 °C, and the conversion of 100%.

The preparation for α-cyano carbonyl carbon compounds in MFCs was divided into two steps: *in situ* formation of organozinc reagent and then cyanidation reaction with cyanoreagents. Processing continuous flow devices of solid-liquid two-phase reactions showed in Fig. 2a. To make 0.1 mol/L 2–bromo-2-methylphenylacetone solution, 1.13 g of 2–bromo-2-methylphenylacetone was liquified in 50 mL of dry DMF solvent. And 1.36 g of *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTs) was dissolved in 50 mL of dry DMF solution to prepare 0.1 mol/L NCTs solution. 2-Bromo-2-methylpropiophe was pumped into the system at a certain flow rate by pump 1 through the packed-bed reactor to the three-way switch. A small amount of outflow liquid was taken from outlet 1 for off-line detection to determine whether the substrate solution was completely transformed into organozinc reagent. Later the switch was turned to allow the organozinc reagent to enter the 3D MFCs (4.3 mL) from outlet 2 to react with NCTs which pumped by pump 2. The final outflow product quenched with a saturated ammonium chloride solution and analyzed by gas chromatograph. All reagents were prepared and added under nitrogen atmosphere during the whole experiment.

Taking into account the successful preparation of the organozinc reagent was the core of the whole experimental results, assembly and activation of packed-bed reactor was an important step (Figs. 2b and c). Detailed steps of filling and activation zinc column were described in Support information. To ensure the accu-

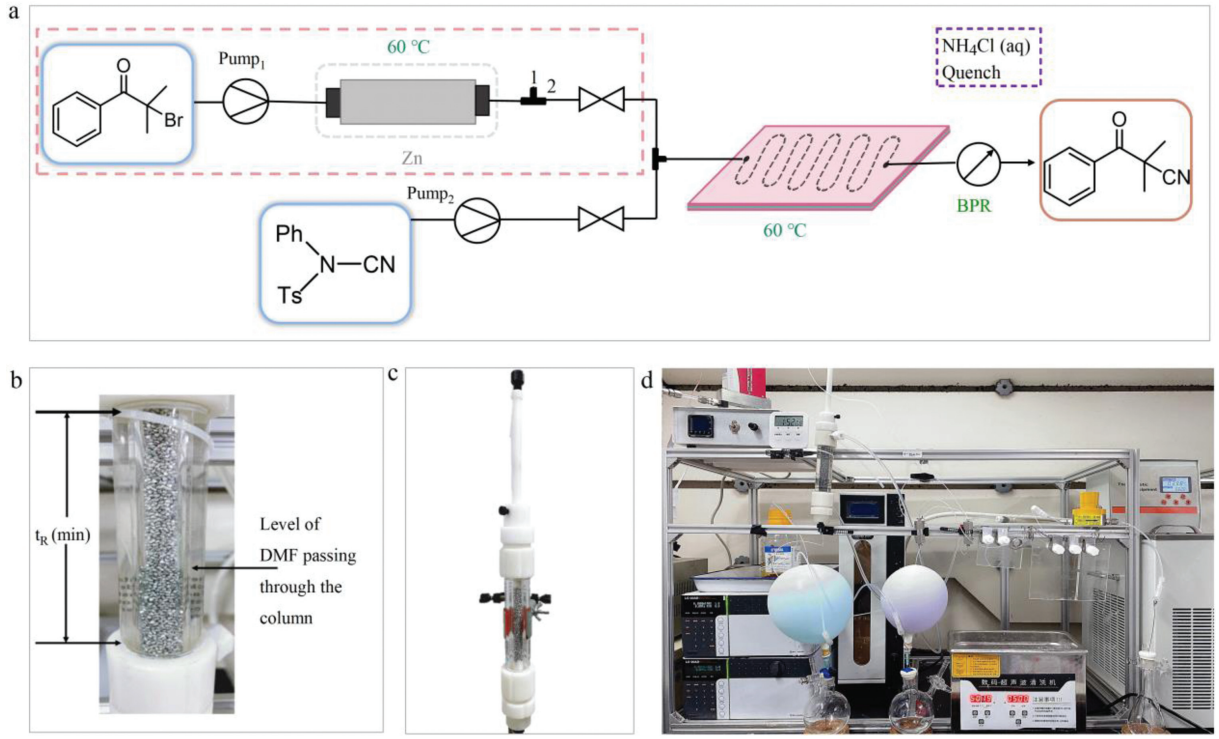


Fig. 2. (a) Schematic of a continuous flow devices of solid-liquid two-phase metal insertion reactions for the preparation of α-cyano carbonyl carbon compounds. (b, c) Photos regarding the setup for packed-bed reactor. (b) Measurement of the packed-bed reactor residence time (t_R). (c) File the column with zinc metal particles. (d) Photo about the setup for a flow MFCs equipment of α-cyano carbonyl compound.

Table 1
The effect of the parameters.

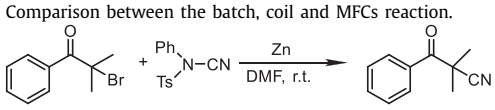
Entry	T_R (min)	Temp$_1$ (°C)	T_2 (min)	Temp$_2$ (°C)	Flow rate (P1) (mL/min)	Flow rate ratio (P1:P2)	Conversion (%)[a]
1	27.5	60	–	–	0.1	–	100
2	13.8	60	–	–	0.2	–	100
3	9.2	60	–	–	0.3	–	100
4	6.9	60	–	–	0.4	–	100
5	5.5	60	–	–	0.5	–	100
6	3.9	60	–	–	0.7	–	100
7	2.8	60	–	–	1	–	86
8	27.5	60	21.4	67	0.1	1:1	100
9	13.8	60	10.7	67	0.2	1:1	100
10	9.2	60	7.1	67	0.3	1:1	100
11	6.9	60	5.3	67	0.4	1:1	88
12	5.5	60	4.3	67	0.5	1:1	78
13	4.6	60	3.6	67	0.6	1:1	46
14	9.2	60	7.1	30	0.3	1:1	10
15	9.2	60	7.1	40	0.3	1:1	41
16	9.2	60	7.1	50	0.3	1:1	52
17	9.2	60	7.1	60	0.3	1:1	100
18	9.2	60	7.1	60	0.3	1:1	100
19	7.6	60	7.1	60	0.36	1.5:1	100
20	6.9	60	7.1	60	0.4	2:1	100

[a] Conversions based on GC-FID analysis of reaction mixture using dodecane as internal standard.

racy conversion of each experiment, the zinc dust should be activated before starting.

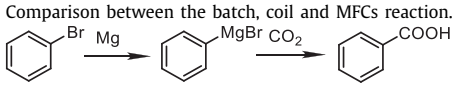
By our previous experimental results and some related reports, the optimal activation temperature of zinc column was 60 °C. The residence time (t_R) for preparation of organozinc reagent was firstly investigated in the range of 2.8–27.5 min (Table 1, entries 1–7). Conversion of the 2–bromo-2-methylpropiophe performed under 3.9–27.5 min showed no difference at 60 °C. A further decrease in residence time to 2.8 min caused the incomplete transformation of 2–bromo-2-methylphenylacetone solution. Then the influence of residence time on the subsequent cyanation reaction was investigated. The flow rate of pump 2 was changed to adjust the residence time of reactants in the MFCs, and the reaction temperature was controlled to be 67 °C. As shown in entries 8–13 in Table 1, 0.3 mL/min displayed the finest yield. And 0.1–0.2 mL/min might be too slow to reduce reaction productivity while that flow rate than 0.4 mL/min resulted in the insufficient reaction time. Next, the influence of reaction temperature on cyanide reaction was explored (Table 1, entries 14–18). The conversion rate varied noticeably after raising the temperature, rising from 10% to 100% as the reaction temperature rose from 30 °C to 60 °C. So the optimal reaction temperature in the range of 30–67 °C was 60 °C. Finally, the effect of the volumetric velocity ratio of the reactants on the cyanation reaction was investigated. The reaction volume flow rate ratio of

Table 2
Comparison between the batch, coil and MFCs reaction.



Parameters	Batch	2D coil	3D MFCs
Temp (°C)	25	60	60
T_1 (min)	–	6.9	6.9
T_2 (min)	–	7.1	7.1
T (min)	120	14	14
Yield (%)	90	60	100
STY (g h^{-1} L^{-1})	1022	68,887.8	114,812.9

Table 3
Comparison between the batch, coil and MFCs reaction.



Parameters	Batch	2D coil	3D MFCs
$Temp_1$ (°C)	50	25	25
$Temp_2$ (°C)	−10–0	25	25
T_1 (min)	25	7	7
T_2 (s)	4800	2.82	2.82
T (min)	33	7	7
Yield (%)	88	45	96
STY (g h^{-1} L^{-1})	1004.8	320,553.5	680,144.4

the organozinc reagent and NCTs substrate could be altered by adjusting the flow rates of the two materials at a total volume flow rate of 0.6 mL/min, 60 °C, and a residence time of 7.1 min. In 3D MFCs, the conditions for the reaction volume velocity ratio were 1:1, 1.5:1, and 2:1, respectively (Table 1, entries 18–20). The gas yield of each flow rate ratio was evaluated when the conversion rate was all 100%. The yield increased from 54.5% at a volume flow ratio of 1:1 to 67.2% at a volume flow ratio of 1.5:1, and to 100% at ratio of 2:1 (Table S3 in Supporting information).

To show advantages of using 3D MFCs system, we compared the conversion of α-cyano carbonyl carbon compounds prepared in different reactors. The supporting information got into further detail on the batch reaction. Under optimized conditions, PTFE tubes with a diameter of 1000 μm and a volume of 4.3 mL were used in the coil microreactor, and Y-shaped three-way joints made of PTFE were used in the mixer. The experimental results were shown in Table 2. The other reaction conditions were exactly the same, where T_1 was the generation time of organozinc reagent. T_2 was the time of the subsequent cyanidation reaction, and T was the sum. Exactly, the space time yield towards MFCs was 112 times higher than batch process. Moreover, many advantages of 3D MFCs devices (Fig. 2d) have also been demonstrated, including the ability to reuse any leftover zinc metal and significantly reduce the need for raw materials; Second, the resulting organozinc reagent could be used right away in the second step of the reaction without preservation, making it possible to avoid contact with air or moisture. Finally, a comparatively pure product solution might be obtained without filtration or dumping. And the ability to prepare the proper amount of organometallic solution on demand, which could strictly control the metal activation and highly exothermic reaction, reduce the risk of reaction, and improve the controllability of the reaction, was one of the flow protocol's main advantages.

Gas-liquid two-phase reaction: As a continuation of the previous work, we continued to build a new gas-liquid two-phase 3D MFCs-involved continuous flow device. This was done in an effort to address issues with the traditional batch reaction, such as its poor mixing effect, harsh reaction conditions, and certain safety threats. The type of metal in the packed-bed reactor was changed in the device, and Grignard reagent was generated *in situ* for carboxylation reaction with carbon dioxide in the 3D MFCs. One of the most widely used reagents in the synthesis of organic chemicals was the Grignard reagent, which could react with electrophiles to create carbon-carbon bonds. It was useful for making a variety of related chemical industries, food, and pharmaceutical intermediates [28]. Halogen/magnesium insertion was one of the most popular options among the preparation of organomagnesium reagents since it was an inexpensive, low-cost, and low-toxic method [29]. However, the exothermic nature of activation might be a problem, and the air sensitivity of the chemicals produced made handling and storage more challenging [30]. There have been some studies using flow chemical devices to effectively solve the above problems. Most halogenated hydrocarbon substrates used in current reports were iodide or bromine. Despite being more cost-effective, chlorine's poor reactivity prevented it from being used in continuous flow chemistry [31]. In order to broaden the variety of substrates, the goal of this work was to create Grignard reagent with benzyl chloride and magnesium metal in a packed bed reactor. A gas-liquid reaction device was also built at the same time using the solid-liquid reaction as a foundation. When used with Grignard reagents, CO_2 may be a plentiful, nontoxic, and renewable source of C_1, which was frequently used to produce carboxylic acid compounds [32]. Nevertheless, due to the high thermodynamic stability and low kinetic reactivity of CO_2, special equipment, such as high-pressure reaction kettle, was usually needed to carry out gas-liquid reaction of CO_2 in the laboratory [33]. To date, gas-liquid two-phase flow reaction between Grignard reagent and CO_2 in microfluidic chips remained as a less explored part and has received rising interest in recent years due to its significant implications for various chemical and pharmaceutical industry [34]. The reports that were already available have certain restrictions. For instance, the low reaction efficiency of tubular microreactors and falling film microreactors coupled with the difficulty of heating the tubular microreactors coupled with the easily blocking the membrane reactor limited the condition optimization of the carboxylation process [35]. Herein the carboxylation reaction involving the Grignard reagent, phenylmagnesium bromide, and CO_2 was used as an example in 3D MFCs device, and the reaction conditions were improved. The successful preparation of benzoic acid, implementation of selectivity, production rate, and safety of process intensification, and has overcome original gas-liquid tubular reactor easy jam, inability heat, and other drawbacks, showed on the great potential of gas-liquid reaction. Optimized, residence time of 2.82 s, which could be in this device at a relatively high yield (96%).

Here we extend our original concept for solid-liquid reaction by using a packed bed filled with magnesium and introducing a gas flowmeter to deliver gas to a substrate stream in a continuous fashion to the 3D MFCs. The gas-liquid flow device was shown in Fig. 3a. Bromobenzene solution was injected into the packed bed reactor using a HPLC pump control unit. *In situ* generation of the Grignard reagent, CO_2 by gas flowmeter controlled into the system, the gas liquid two phase in the volume of 1.9 mL of 3D MFCs reaction (Fig. 3b). BPR was used to maintain pressure in the system and prevent gas from escaping, allowing the two reactions to be more adequate. After each experiment, BPR must be adjusted to release exhaust gas to ensure that the system was in a pressure stable state. The outflow liquid quenching with HCl, and the use of a gas chromatograph with tridecane as internal standard to analyze the yield of product were all carried out in this process.

The assembly process of the magnesium packed-bed reactor was the same as that of the zinc column, but the mass, dead volume and residence time of the magnesium packed-bed were different. The detailed description was in Support information. The key stage in the effective synthesis of Grignard reagent was the activation of magnesium. The most typical activation technique involved dissolving the magnesium oxide on the surface with acid,

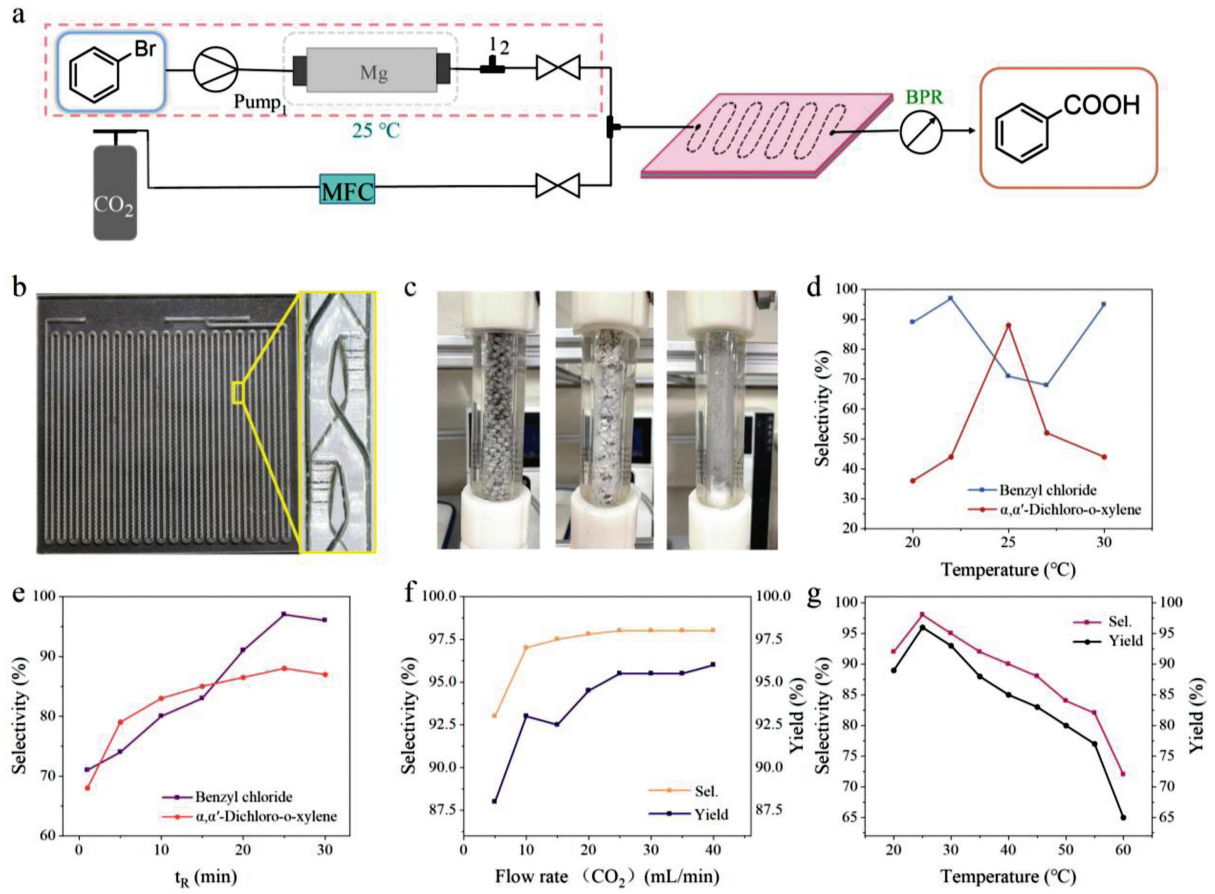


Fig. 3. (a) Processing continuous flow MFCs devices of gas-liquid two-phase reactions for the preparation of carboxylic acid compounds. (b) Photograph of the microfluidic chip. (c) Reaction of magnesium particles with 16–20 mesh size, magnesium turnings, magnesium powder, from left to right, with halogenated hydrocarbons, a certain amount of white precipitate was observed at the column and pipe outlet in the first two specifications of magnesium, The effect of the parameters: (d) temperature for solid-liquid two-phase reactions, (e) residence temperature for solid-liquid two-phase reactions, (f) flow rate of the CO_2, (g) temperature for gas-liquid two-phase reactions.

exposing the magnesium to the halogenated hydrocarbon for reaction. To our surprise, magnesium and acid reacted forcefully, especially in a glass column, a significant volume of gas was produced, which leaded to an abrupt rise in pressure and runaway reactions. Through research and testing [31], it was discovered that using 1–bromo-2-chloroethane as the initiator and TMSCl and DIBAL-H as the activators could safely remove both magnesium oxide and water from the system. In a nitrogen atmosphere, 0.4 mL of 1–bromo-2-chloroethane solution, 1.6 mL of TMSCl solution, 9 mL of DIBAL-H (toluene as solvent) and 9 mL of dried THF solution were prepared into 20 mL of activation solution. The activated solution was pumped through the magnesium column at a flow rate of 1 mL/min, and the pump was turned off after 20 min when a large number of bubbles were observed. First, we investigated the impact of magnesium metal particle size and state on the rate of Grignard reagent conversion (Table S4 in Supporting information). Large magnesium metal particles had a relatively low specific surface area, which may result in a low conversion efficiency, while small powder particles may cause a high system back pressure or clog the filter device. We found that when magnesium particles with 16–20 mesh size or magnesium turnings were used, a certain amount of white precipitate was observed at the magnesium column and pipe outlet, leading to system plugging and no product formation (Fig. 3c). The reason was that the solubility of organic magnesium reagent was relatively low, which would form a passivation layer on the surface of metal and reduce the metal insertion rate. Following testing, magnesium powder with a mesh size of 20–230 was found to be the most suitable. Its reaction process did not produce white precipitation, and its moderate particle size prevented the system pressure from rising while maintaining a high specific surface area, effectively enhancing the contact area between metal and halogenated hydrocarbon.

Under nitrogen atmosphere, 0.575 mL of benzyl chloride was dissolved in 50 mL of dry THF solvent to prepare 50 mL of 0.1 mol/L benzyl chloride solution. The same method was used to prepare α,α'-dichloro-*o*-xylene Grignard reagent. The Grignard reagent for benzoyl chloride was easily hydrolyzed or coupled to yield a high number of by-products, which could be decreased by regulating the reaction temperature. The Grignard reagent could be completely transformed from the benzyl chlorides when the residence time was 30 min, but at different temperatures, the product selectivity varied (Fig. 3d). It was evident that the selectivity rose as the temperature rose, but when the temperature surpassed a specific point, the reaction's selectivity sharply dropped and more coupling byproducts were produced. The ideal temperature for the benzyl chloride was therefore 22 °C. α,α'-Dichloro-*o*-xylene was more sensitive to temperature and had more by-products. At 22 °C, a significant portion of α,α'-dichloro-*o*-xylene produced 2-methylbenzyl alcohol as a by-product, only a minor portion produced the coupled by-products. However, a significant number of coupling by-products were produced at 30 °C. The selectivity was considerably increased to 88% only at 25 °C. It suggested that the homogeneous temperature and heat dissipation capacity of the packed-bed reactor may effectively solve the problems of increasing by-products and unstable selectivity caused by the uneven heat release in the batch reaction. Once the temperature of

the Grignard reagents had been optimized, the residence time of this methodology was studied (Fig. 3e). The best residence time of Grignard reagent prepared from benzyl chloride and α,α'-dichloro-*o*-xylene were both 25 min.

Then the use of gas-liquid two-phase continuous flow reaction was explored. Bromobenzene (0.1 mol/L, 100 mL) was passed through the magnesium packed-bed reactor at a flow rate of 0.5 mL/min. On the other hand, CO_2 was controlled by gas flowmeter, and the two phases flowed through the one-way valve to mix and react fully in the 3D MFCs. At the same time, the back pressure of the whole system was controlled to be 0.2 MPa, and the CO_2 gas flow rate was taken as the total flow rate after mixing. Because the gas flow rate was 10–80 times of the liquid flow rate in the reaction process, the liquid flow rate was usually ignored. When the liquid flow rate of bromobenzene was 0.5 mL/min, the temperature was 25 °C, and the back pressure was 0.2 MPa, the reaction was investigated at different flow rates of CO_2, and the experimental results were shown in Fig. 3f. When the gas flow rate was 40 mL/min and the residence time was 2.8 s, the selectivity and yield were 98% and 96%, respectively. Increasing the flow rate would increase the effective concentration of CO_2 in the MFCs and an effective increase in the yield in a shorter time. After it was established that 40 mL/min was the appropriate flow rate for CO_2, the impact of temperature on the gas-liquid reaction was examined while maintaining the same pressure and flow rate (Fig. 3g). The selectivity and yield of benzoic acid rose from 92% and 89% to 98% and 96%, respectively, when the temperature was raised from 20 °C to 25 °C. The yield and selectivity did, however, drastically decline as the temperature climbed. For example, when the temperature went from 30 °C to 60 °C, the selectivity and yield went from 95% and 93% to 72% and 65%, respectively. The drop in yield may be caused by the fact that CO_2 became less soluble in substrate solution as temperature rose.

We further evaluated the reaction efficiency in the traditional batch and the microreactors. The 2D coil microreactor used PTFE tubes with a diameter of 1000 μm and a volume of 1.9 mL and contained a Y-type three-way mixer. The reaction conditions were consistent with the optimized results of the 3D MFCs. The supporting information got into further detail on the batch reaction. The reaction time of carboxylation reaction in 3D MFCs flow systems was 7 min which observed to be shorter than those in the bath systems. Benzoic acid in the 3D MFCs continuous flow device reached a steady yield of 96% with the STY of 680,144.4 g h^{-1} L^{-1}, much higher than that of batch reaction (88%, 1004.8 g h^{-1} L^{-1}) and 2D coil reaction (45%, 320,553.5 g h^{-1} L^{-1}). It was demonstrated that, in comparison to the conventional reaction, our device not only significantly increased selectivity but also successfully expanded the range of substrate. A gas-liquid two-phase continuous flow device was successfully built on the basis of solid-liquid two-phase reaction, and the reaction between the *in-situ* produced magnesium phenyl bromide Grignard reagent and CO_2 in the 3D MFCs was realized. Only a limited number of reagents are combined at any one time, and the generated product can be employed right away for further reactions in subsequent chemical reactions. We proposed that the manufacturing risk and storage challenge of the Grignard reagent would be significantly reduced by our 3D MFCs with a continuous flow system, resulting in a long-term, highly effective *in situ* formation and Grignard reagent usage.

In conclusion, using femtosecond laser micromachining, we have created novel 3D MFCs that can effectively mix materials in various channels for chemical synthesis. It epitomizes the operational downsizing, the high degree of integration, the fact that our synthetic protocol occupies less space and saves a lot of resources. A new, simplified, cost-effective, and risk-free flow synthetic equipment is established for large scale organic synthesis by MFCs using examples from the liquid-liquid, solid-liquid and gas-liquid two-phase synthesis. High yield, rate, and selectivity are highlighted by the device, along with the benefits of green, safe, mature, and steady performance. Due to the threat associated with storing and collecting significant volumes of material are eliminated, our 3D MFCs' technology has shown to be well adapted for the continual on-demand generation of potentially hazardous, reactive, or explosive intermediates. It is more affordable, widely used, ecologically friendly, of higher quality, and has a variety of additional advantages over commercial continuous flow synthesis devices. The future is expected to solve the bottleneck problems in organic synthesis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2022.107985.

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