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PAPER

Interfacial organic synthesis in a simple droplet-based microfluidic system†

Ji Ji,[a] Yiqing Zhao,[a] Liping Guo,[a] Baohong Liu,*[a] Chang Ji[b] and Pengyuan Yang*[a]

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A spherical liquid–liquid interface can be obtained by dispersing one liquid phase into another to form droplets, which will facilitate the two-phase reactions between the immiscible participating fluids. The phase transfer catalysts assembled at the droplet "wall" catalyze the reactions between the aqueous and organic phases. The study illustrates an interfacial synthetic approach which is ideal for the biphasic reaction by taking advantage of the droplet-based microdevice. The improved reaction efficiency can be attributed to the high surface-to-volume ratio and internal flow circulation in the droplets.

Introductions

The interface between two immiscible liquids offers a scaffold for the controlled formation of thin layers with various compositions, where different chemical reactions may occur. For example, both self-assembly with subsequent cross-linking of nanoparticles[1] and direct polymerization[2] can take place at liquid–liquid interfaces. In recent years, multiphase catalytic reactions have played more significant roles not only in the research laboratory but also in the chemical and pharmaceutical industries.[3] They are often classified by the various phases involved, such as liquid–liquid, gas–liquid, gas–liquid–liquid, or gas–liquid–solid reactions. Although numerous multiphase reactions have been reported, many of them are still difficult to carry out when compared to homogeneous reactions. In most cases, the efficiency for the interaction and mass transfer between different phases is extremely low and thus causes very slow reaction rates. In order to accelerate the multiphase reactions, treatments such as vigorous stirring are needed to create higher interfacial area between the two or three reacting phases. To improve this problematic process, the development of a more effective and yet simple device is particularly desired. For example, Kobayashi and co-workers developed an efficient system for the triphasic reactions using a microfluidic reactor, where the hydrogenation of unsaturated carbon–carbon bonds can proceed smoothly to afford the desired products quantitatively within two minutes for a variety of substrates.[3]

A spherical liquid–liquid interface can be obtained by dispersing one liquid phase into another to form droplets, which will facilitate the two-phase reactions between the immiscible participating fluids.[4] The droplet-based microfluidic systems can also provide many different ways to execute reactions on a small scale.[5] Droplets of the dispersed phase are usually produced by the shear force and interfacial tension at the fluid–fluid interface.[6] T-junction and flow-focusing techniques have been used to generate droplets in microfluidic channels. Applications of droplet-based microfluidic systems include chemical and biochemical screening,[7] synthesis of various materials,[4] assays for cells,[8] as well as drug discovery and delivery.[9] Generating discrete droplets in an immiscible continuous phase (carrier phase) allows reactions to be compartmentalized into femtolitre to nanolitre volumes. In essence, each droplet is analogous to the conventional reaction flask but with the advantages of reduced reagent consumption,[10] rapid mixing,[11] automated handling,[12] and continuous processing.[13] Consequently, droplet-based microfluidic systems have been used for a variety of organic reactions. Moreover, it is well known that the high surface-to-volume ratio inherent to small droplets, and the internal flow circulation in droplets can significantly enhance mass transfer between dispersed and carrier phases in microfluidic channels. Several research groups have utilized this technique to facilitate various phase-transfer reactions. Onal *et al.*[14] reported a three-phase hydrogenation reaction using organic droplets and hydrogen gas bubbles dispersed in an aqueous catalytic stream. Phase-transfer mediated nitration,[15] Claisen–Schmidt condensation,[16] and hydrolysis reactions[17] have also been carried out using droplet-based microfluidic devices. More recently, Huck and his colleagues[18] designed several droplet reactors with catalytically active walls for the synthesis of small molecules.

To achieve more efficiency in liquid–liquid interfacial reactions, we fabricated a simple microfluidic device consisting of a flow-focusing junction, as shown in Scheme 1a. The operation of the device will be discussed in detail subsequently. The idea is to make use of microdroplets formed in the channels to facilitate the two-phase reaction process. If the aqueous solution containing phase transfer catalyst (PTC) is used as carrier phase and the organic reagent (without solvent) is employed as dispersed

[a]*Department of Chemistry and Institutes of Biomedical Sciences, Fudan University, 220 Handan Road, Shanghai, 200433, China. E-mail: pyyang@fudan.edu.cn; bhliu@fudan.edu.cn; Fax: +86 21 65641740*
[b]*Department of Chemistry and Biochemistry, Texas State University, 601 University Drive, San Marcos, Texas, 78666, USA*
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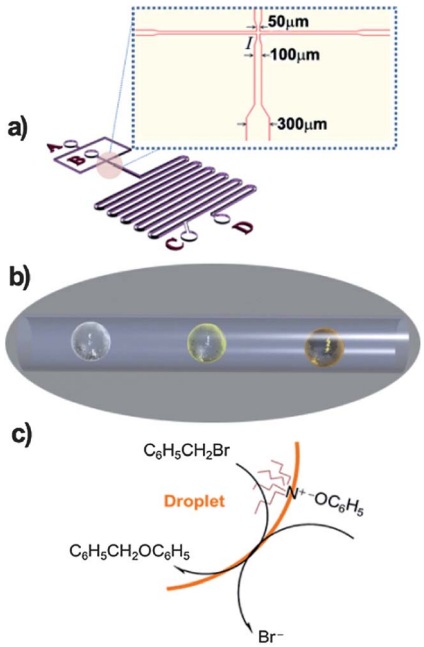


Scheme 1 Schematic representations for the droplet-based interfacial microreactor. a) Overview of the microfluidic chip device. Both immiscible liquids are supplied by syringe pump to a flow-focusing cross point (*I*), where formation of organic droplets in the aqueous carrier phase takes place. The flow rates of both solutions can be adjusted independently. b) Product is formed as the droplets flow through the microchannels. c) The PTCs, as surfactants, self assemble at the liquid–liquid interface to catalyze the reactions between the aqueous and organic phases while the organic droplets travel through hydrophilic microchannels.

phase, the oil-in-water droplets can be generated by the shear force and interfacial tension.[6] When placed in the carrier phase, PTC could also assemble on the surface of the droplets and speed up the reactions between the two phases.[19] When compared to conventional dispersion techniques, our microdevice offers faster interfacial reactions, as more effective mass transfer is expected due to the high surface-to-volume ratio and internal flow circulation in the droplets.

To test our microfluidic system, we chose the synthesis of benzyl phenyl ether catalyzed by TBABr (tetrabutylammonium bromide, used as PTC) as the model liquid–liquid reaction, which is between benzyl bromide as the organic phase and phenoxide in aqueous phase. PTCs are usually surface-active species that can transfer reactants between immiscible phases and also help to disperse one phase into the other. The PTC catalyzed two-phase reaction is a rapidly growing method with significant commercial benefits and capabilities for producing speciality organic compounds.[20]

Results and discussion

Our microfluidic device was fabricated by soft-lithography technique[21] and polydimethylsiloxane (PDMS) was used as the base material to form microchannels 100 μm in height. The general design and dimensions of the device can be found in Scheme 1a. Channel wettability, which impacts on the type of drops formed in the microfluidic device, is the most important parameter and should be carefully controlled.[22] Water drops in oil are more easily formed if the channels are hydrophobic, whereas oil drops in water are likely formed if the channels are hydrophilic. Therefore, the hydrophobic surface of PDMS are usually tuned to hydrophilic, creating an effective wetting of the channels so that oil-in-water drops can be produced more efficiently. Various surface modification techniques have been reported including chemical vapor deposition,[23] covalent surface modification,[24] sol–gel method,[25] and layer-by-layer deposition.[26] We used layer-by-layer approach to obtain stable hydrophilic coatings on PDMS microchannels and the detailed procedures can be found in the experimental section. The poly(diallyldimethylammonium chloride) (PDDA) solution was introduced into channels when the negative charges, generated by plasma bonding,[27] were still present on PDMS surface. Consequently, a layer of the positively charged polyelectrolyte could be formed. Subsequently, the poly(sodium 4-styrenesulfonate) (PSS) polyanions flushed through channels would deposit on the PDDA layer. A hydrophilic coating for the microchannels was produced after three layers of PDDA/PSS assembly were deposited.

The liquid–liquid interfacial reaction was carried out on this home-customized chip as a droplet-based microdevice, as shown in Scheme 1a. The flow-focusing technique was employed to obtain monodisperse droplets. A phenoxide solution was prepared by dissolving phenol into aqueous NaOH and used as the carrier phase with a lower interfacial tension in hydrophilic channels. This aqueous solution was injected into port A (Scheme 1a) connected with two side channels on the device. Pure benzyl bromide ($C_6H_5CH_2Br$) without any solvent was injected as the dispersed phase into Port B (Scheme 1a) linked with the central channel. The two phases would meet at the cross point, *I* (Scheme 1a), to generate uniform oil-in-water droplets. It should be noticed that the contact between the organic phase and the surface of PDMS chip is minimal as the droplets travel in aqueous phase through the microchannels. Thus the permeation of organic species into PDMS base is not significant in this method. However, for an extensive employment of PDMS microfluidic chip in organic synthesis, more efficient surface modification methods are necessary to prevent the permeation of organic compounds into PDMS. The nucleophilic reaction between benzyl bromide and phenoxide took place at the interface while the droplets moved through the hydrophilic microchannels (approximately 17 cm in length). Eventually, the reaction was quenched with acetic acid solution, which was injected into Port C (Scheme 1a). Benzyl phenyl ether was quantitated by collecting the product from the outlet (Port D, Scheme 1a) of the microfluidic reactor, followed by offline analysis with the aid of HPLC. If the residence time of the droplets in the channels could be translated into reaction time, the kinetics of the reaction might be monitored by either changing the total flow rate of the fluids or the length of the microchannel.[28]

TBABr was also added to the carrier phase in the system for two reasons. First, TBABr can act as PTC to catalyze the model interfacial reaction. Second, in order to form reliable droplets, as shown in Scheme 1b, the microfluidic device requires some water-soluble surfactants to reduce the surface tension at the aqueous–organic interface.[19] TBABr, acting as a surfactant, can arrange at

the water–oil interface with the polar functional group in the aqueous phase and the alkane tail in the organic phase (Scheme 1c). Consequently, the oil-in-water droplets can be formed more easily and remain stable in the channels.

Phenoxide reacted rapidly with benzyl bromide in our droplet-based microfluidic device to afford 95% conversion to benzyl phenyl ether within a minute at room temperature (Table 1, Entry 2) using aqueous/organic phase flow rates of 200/100 μL h^{-1}. For conventional synthetic process involving vigorous stirring of the two immiscible phases, benzyl phenyl ether was obtained in 96% conversion (Table 1, Entry 1) but the reaction took several hours. Comparatively, the percentage conversion to ether would be just 18% within one minute for the bulk reaction (see Fig. S1. ESI†). Other substrates were also studied using the microdevice, with alteration of the aqueous/organic phase flow rates in order to form the reliable droplets with optimized reaction conditions, considering the different physical properties between phenol and *p*-cresol (as well as benzyl bromide and benzyl chloride). As presented in Table 1, the percentage conversions to ethers for the reactions between deprotonated *p*-cresol and benzyl bromide or benzyl chloride at 45 °C were 51% (Entry 4) and 50% (Entry 6), respectively, within 30 s and 36 s of residence time in the microchannels. To achieve similar results, the bulk two-phase reactions took at least 30 min (Entries 3 and 5), which were much slower than our reaction system. These data clearly indicate that the efficiency of mass transfer between the two phases is greatly improved by the microfluidic device for liquid–liquid interfacial reactions, when compared to conventional dispersion technique. Meanwhile, the results also show that our protocol can be potentially applied for more difficult nucleophilic substitution reactions which are carried out at a higher temperature. The enhancement is mainly due to the high surface-to-volume ratio and internal flow circulation for the droplets formed in microchannels.[6]

Since the biphasic synthesis is based upon the encounter of substrates at the interface of two immiscible solutions, the nature of the interfacial layer is of great importance for the reaction efficiency. Moreover, it should be noted that phenoxide concentration in organic phase would also increase in the presence of PTC to speed up the nucleophilic substitution. The dimension of the droplets, which determines the area of the interface and consequently may affect the percent conversions to products, can be controlled over a limited range by adjusting the aqueous/organic phase flow rates.[29] In this investigation, the effect of flow rates of both carrier and dispersed phases on droplet size was examined. As shown in Fig. 1, the droplet size gradually decreases with increased flow rates of the two phases. At higher flow rate, the frequency for the generation of droplets appears to be lower in Fig. 1 but in fact more droplets are produced in the microchannels. This is because in order to obtain the clear micrographs in Fig. 1, the microfluidic device had to be moved under the microscope in the opposite direction of the flowing droplets at a suitable velocity (a < b < c), which is dependent upon the feeding flow rate. Umbanhowar and his colleagues[29] developed a simple technique to precisely control the droplet size by changing the velocity of the carrier phase. They believed that the droplet size is a comprehensive function of the carrier phase flow rate, the extrusion rate, and the viscosities and interfacial tension of the two phases. Table 2 presents the data for the change in percentage conversions with aqueous/organic phase flow rates. The percent conversion to benzyl phenyl ether would decrease (from 95% to 71%) with slower aqueous/organic flow rates (from 200/100 μL h^{-1} to 80/40 μL h^{-1}), which lead to the formation of larger droplets with lower surface-to-volume ratio as well as longer residence time in the microreactor

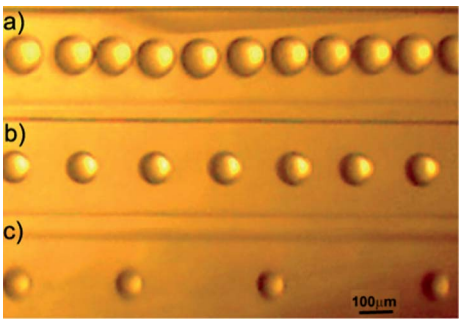
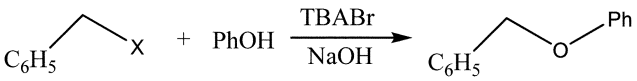


Fig. 1 Optical micrograph of droplets formed in microchannels with aqueous/organic phase flow rates at a) 80/40 μL h^{-1}, b) 160/80 μL h^{-1}, and c) 200/100 μL h^{-1} for the synthesis of benzyl phenyl ether.

Table 1 The interfacial synthesis of ethers in droplet and bulk solutions



Entry	$C_6H_5CH_2X$	PhOH	Time	*T* (°C)	Percent conversion (%)[f]
1[a]	X = Br	C_6H_5OH	180 min	25	96
2[b]	X = Br	C_6H_5OH	1 min[c]	25	95
3[a]	X = Br	*p*-$CH_3C_6H_4OH$	45 min	45	68
4[b]	X = Br	*p*-$CH_3C_6H_4OH$	30 s[d]	45	51
5[a]	X = Cl	*p*-$CH_3C_6H_4OH$	30 min	45	50
6[b]	X = Cl	*p*-$CH_3C_6H_4OH$	36 s[e]	45	50

[a] Aqueous phenoxide/TBABr was added to a vigorously stirred benzyl halide liquid. [b] Droplet-based microdevice was used for liquid–liquid interfacial reaction. The aqueous/organic phase flow rates are: [c] 200/100 μL h^{-1}. [d] 600/200 μL h^{-1}. [e] 600/80 μL h^{-1}. [f] Percent conversions were determined by HPLC.

Table 2 The effect of aqueous/organic phase flow rates on percent conversions to benzyl phenyl ether by using the droplet-based microdevice

Entry	Aqueous/organic flow rates (μL h^{-1})	Residence time (min)	Percent conversion (%)
1[a]	200/100	1.0	95
2[a]	160/80	1.2	85
3[a]	80/40	2.3	71
4[a]	40/20	4.6	80

[a] The temperature for the liquid–liquid interfacial reaction is 25 °C.

(Entries 1–3), and overall less efficient reactions. However, at a further lower aqueous/organic flow rate of 40/20 μL h^{-1}, the prolonged residence time (4.6 min) could bring the percentage conversion back up (Entry 4). In general, it is obvious that high aqueous/organic flow rates in the microdevice will generate small size droplets with high surface-to-volume ratio, which can improve mass transfer at the liquid–liquid interface. Additionally, higher flow rates can also enhance internal flow circulation in droplets, causing higher reaction rates to give more products within a shorter period of time. The highest aqueous/organic flow rates reached in our microfluidic system is 200/100 μL h^{-1} for the synthesis of benzyl phenyl ether, while still maintaining a stream of stable and uniform droplets. Improvement might be possible by adjusting the dimension of the microchannels.

Given the intrinsic nature of microdroplets, the interfacial synthesis by using our approach can be extended to other two-phase reactions and applications for making unique micro- or nanomaterials.[4,30] For example, our protocol may be used for the conversion of oxiranes to thiiranes[31] and the alkylation of *N*-diphenyl methylene glycine esters.[20] Besides the high reaction efficiency the microdevice can provide, the technique may also possess several other advantages. The reaction can be scaled up by using a number of chips in parallel with shared flow to match the throughput of batch reaction. It is not uncommon to obtain gram to kilogram quantities of products per day by running multiple microreactors in parallel.[32] Using the data in Table 1, Entry 2, a simple calculation shows that 10 mL of benzyl bromide can be converted to benzyl phenyl ether per hour if 100 chips are connected in parallel. This productivity is at least comparable to the bulk reaction, if not better. Moreover, the pure products (*i.e.* benzyl phenyl ether) can be collected within a short period of time as the interfacial reaction is continuous in our microdevice and this benefit is not offered by the bulk reaction. The catalytically active aqueous phase could be recycled in an uninterrupted fashion and pure products can also be easily isolated by selectively patterned microchannels.[33] Several methods have been reported for these purposes to separate the aqueous and organic phases by droplet extraction. Kennedy's group[34] employed and modified a segmented phase channel to be hydrophobic to significantly stabilize the phase boundary during the droplet transferring process. A novel droplet extraction interface based on hydrophilic tongue structure with a back pressure regulator was developed by Fang and his co-workers[35] to transfer droplets from segmented phase to aqueous phase more reliably. Future experiment would incorporate the reagent separation technology into our microfluidic device to build up a fully automated system which is capable of performing a wide array of reactions with minimal amounts of catalyst. Furthermore, it will also be a green reactor for testing biphasic interfacial synthesis since least amounts of organic compounds are consumed.

Experimental

Regents

Poly(diallyldimethylammonium chloride) (PDDA) and poly-(sodium 4-styrenesulfonate) (PSS) were purchased from Sigma-Aldrich. Benzyl halides, phenol, *p*-cresol, and tetrabutylammonium bromide (TBABr) were of analytical grade and purchased from Shanghai Chemical Reagents Co. (Shanghai, China). All reagents were used as received without further purification.

Device fabrication

The microfluidic device was made by conventional soft lithographic techniques.[21] The basic architectures were designed with AutoCAD and transferred to high-resolution photomasks fabricated on transparencies. The negative photoresist SU-8 2035 (Microchem) was spin-coated onto 3 inch silicon wafers which were subsequently patterned using a MJB4 mask aligner. Development was accomplished by immersion in 1-methoxy-2-propyl acetate (Sigma-Aldrich).

A commercially available RTV615 PDMS kit (Momentive) containing the pre-polymer and a cross-linker was used in the recommended ratio of 10 : 1 (w/w). The mixture was poured on top of the patterned silicon wafers and degassed. After curing at 80 °C for 2 h, the PDMS cast was cut and peeled off from the wafers. Microfluidic channel inlets and outlets were stamped out using a biopsy punch with an outer diameter of 2 mm. The microdevice was assembled by attaching the PDMS cast to a glass slide. The bonding strength was provided by pre-treating the contact surfaces with oxygen plasma for 60 s in the plasma cleaner (PDC-32G, Harrick Plasma).

Surface modification

Hydrophilic channel coatings were prepared by layer-by-layer method. After plasma bonding, aqueous solutions of PDDA (3 mg mL^{-1}, containing 0.13 M sodium chloride and 0.005 M ammonia), PSS (0.1% w/v in 0.5 M NaCl solution), and 0.1 M NaCl were pumped sequentially for three times into the microchannels *via* a poly(ethylene) tube, using a syringe pump with a constant flow rate of 100 μL h^{-1}. The treatment was completed by a final washing step with deionized water to remove residue salts from the channel walls. Each solution was kept inside the channels for 20 min.

Microfluidic experiments and bulk reactions

All liquids were pumped into the microfluidic devices *via* poly(-ethylene) tubing without priming prior to the experiments. Multichannel syringe pumps (LONGER Apparatus, Shanghai) were used to accurately inject liquids at constant flow rates. The reaction temperature was set and controlled by a heating plate (QiangQiang, Shanghai), on which the microdevice was placed.

The oil-in-water droplets were formed in microfluidic reactor by flow-focusing technology using pure benzyl halide as

dispersed phase and aqueous solution containing 10 mol L^{-1} NaOH, 7.5 mol L^{-1} phenol or *p*-cresol, and 0.15 mol L^{-1} TBABr as carrier phase. The product was generated as the droplets flowing through the microchannels. The nucleophilic reaction was quenched with acetic acid solution. The mixture collected at the microdevice outlet was diluted with CH_3CN and injected into HPLC (Agilent 1100). For HPLC analysis, the separation was carried out on a HP Stable Bond-C_{18} (4.6 mm × 250 mm, 5 μm) column using a mobile phase of 15% water and 85% CH_3CN at a flow rate of 0.8 mL min^{-1}. Droplet images on the chip were captured by using a microscope with CCD (moticcam 2005, 2.0 M pixel).

For bulk reactions, the concentrations of substrates in two phases were the same as those used in microfluidic reactions. A 5.0 mL of aqueous solution containing 50.0 mmol of NaOH, 37.5 mmol of phenol or *p*-cresol, and 0.75 mmol of TBABr was added to 25 mmol (about 3 mL) of benzyl halide with vigorous stirring (stirred with a 1-cm bar at 650 rpm) in 25-mL round bottom flask. The product mixture was extracted with diethyl ether and the combined organic phases were dried over anhydrous $MgSO_4$. After filtration, the solvent was removed under vacuum and the residue was dissolved in CH_3CN to be analyzed by HPLC. All conversion percentages were calculated with regard to benzyl halides.

Conclusions

In summary, the results presented in this paper illustrate an interfacial synthetic approach which is ideal for the biphasic reaction by taking advantage of the droplet-based microdevice. The differences in solubility, shear force, and interfacial tension of the aqueous and organic species enable the self-completing formation of microdroplets. The PTCs assembled at the droplet wall catalyze the reactions between the aqueous and organic phases. When compared to conventional dispersion technique, our microfluidic system delivers efficient liquid–liquid reactions due to more effective mass transfer between the two phases, which can be attributed to the high surface-to-volume ratio and internal flow circulation in the droplets. To our best knowledge, this is also one of only a few examples[15–17] that have shown biphasic reactions which do not require any modifications of catalysts in the microreactors. Potentially, the approach can be adapted to a wide range of multiphasic reactions, which may stimulate more interest in using the droplet-based microdevice for various interfacial syntheses.

Acknowledgements

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