VIP Synthetic Methods Very Important Paper

International Edition: DOI: 10.1002/anie.201612308
German Edition: DOI: 10.1002/ange.201612308

Two-Phase Reactions in Microdroplets without the Use of Phase-Transfer Catalysts

*Xin Yan, Heyong Cheng, and Richard N. Zare**

Abstract: *Many important chemical transformations occur in two-phase reactions, which are widely used in chemical, pharmaceutical, and polymer manufacturing. We present an efficient method for performing two-phase reactions in microdroplets sheared by sheath gas without using a phase-transfer catalyst. This avoids disadvantages such as thermal instability, high cost, and, especially, the need to separate and recycle the catalysts. We show that various alcohols can be oxidized to the corresponding aldehydes and ketones within milliseconds in moderate to good yields (50–75 %). The scale-up of the present method was achieved at an isolated rate of 1.2 mg min^{-1} for the synthesis of 4-nitrobenzylaldehyde from 4-nitrobenzyl alcohol in the presence of sodium hypochlorite. The biphasic nature of this process, which avoids use of a phase-transfer catalyst, greatly enhances synthetic effectiveness.*

Organic reactions in systems containing two immiscible liquid phases appear in a number of important applications in chemical, pharmaceutical, and polymer synthesis.[1] The reaction between two substances located in different phases of a mixture is often inhibited because of the inability of reagents to come together. Traditionally, a phase-transfer catalyst (PTC) is used to enhance reaction rates, making feasible a wide range of synthetic reactions not possible in a single phase.[2] The most common arrangement for PTCs involves the transport of a water-soluble reactant into an immiscible organic solvent (Starks extraction mechanism[3]) or the transport of a reactant at the interface of two immiscible solvents (Makosza interfacial mechanism[4]) with an appropriate hydrophobic phase-transfer catalyst. Two-phase reactions are carried out between immiscible phases; thus, the nature of the interface and the physical properties of the reacting compounds at the interface become very important in promoting the desired reaction at a satisfactory rate. Methods that can increase the interfacial contact area between the two phases should effectively improve mass transfer, resulting in better product conversion in less time.[5] Available methods such as vigorous magnetic or mechanical stirring,[6] ultrasonic irradiation,[7] and use of a rotor-stator homogenizer[8] accelerate two-phase reactions to some extent, but a phase-transfer catalyst is still necessary in those methods.

Therefore, using current methods, one cannot avoid problems associated with phase-transfer catalysts, such as thermal instability, cost, and, especially, the need to separate and recycle the catalysts.[9] PTCs for anions are often quaternary ammonium salts (Q^+). The recovery is usually accomplished by extraction, distillation, adsorption, or binding to an insoluble support.[10] Most methods employ an organic layer containing about 90 % Q^+, which must be recycled at least ten times with no loss of Q^+.[9] Removing residual traces of Q^+, usually by ion-exchange, can be difficult and expensive, but it is often required for the synthesis of drugs and Q^+-sensitive products.[9] We present a methodology that avoids using a phase-transfer catalyst but still enables the two-phase reaction to occur within milliseconds in yields of 50–75 %.

Recent studies have shown many single-phase reactions can be dramatically accelerated in microdroplets[11] created by spray-based ionization,[12] surface drop-casting,[13] and microfluidics.[14] Microdroplets as microreactors have a strikingly different reactive environment from that of the corresponding bulk phase.[15] How exactly the reaction is accelerated in microdroplets, however, remains to be fully understood, given both the size and time scales involved. Many factors are thought to contribute to the reaction acceleration such as microdroplet evaporation, confinement of reagents, alteration of pH of the microdroplet surface, and probably one of the most important features, the high surface-to-volume ratio of the microdroplet.[11] A reaction/adsorption model describing adsorption of molecules at interfaces in small droplets plays an important role in reaction acceleration in microdroplets.[14] The observation of additional acceleration for *p*-methylbenzaldehyde in a microdroplet reaction with 6-hydroxy-1-indanone by cooperative interactions between *p*-methylbenzaldehyde and *p*-nitrobenzaldehyde supported the above model based on the assumption that more reagents stayed at the interface than in the bulk.[16]

In this work, we provide a strategy for performing superfast two-phase reactions in microdroplets without using a phase-transfer catalyst. A bulk liquid–liquid system was dispersed as small aerosol droplets so that the interfacial area between the two phases is increased by many orders of magnitude.[15] We also used the extreme case, reactions that only occur at the interface, to elucidate the important role of the microdroplet interface in two-phase reaction acceleration. Stevens oxidation[17] without using a phase-transfer catalyst (Scheme 1) was chosen as a proof of concept. Sodium hypochlorite (NaOCl) was used to oxidize 4-nitrobenzyl alcohol (**1**) to 4-nitrobenzaldehyde (**2**).

Figure 1 a shows our experimental design. Two high-speed streams of microdroplets of **1** (0.2 M) in ethyl acetate (EtOAc)

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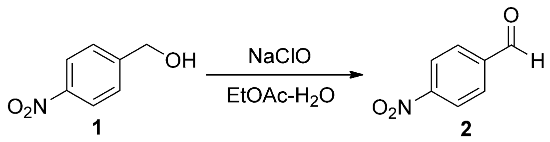
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: http://dx.doi.org/10.1002/anie.201612308.



Scheme 1. Stevens oxidation of 4-nitrobenzyl alcohol (**1**) with NaClO in ethyl acetate and water to form 4-nitrobenzaldehyde (**2**) without using a phase-transfer catalyst.

and NaOCl (12.5%) in water were generated by the nebulization of the respective bulk solutions with a turbulent gas (N_2). Oxidation was initiated by the rapid mixing of droplets containing each reactant at the spray emitters and progressed as the microdroplets travelled through the air. The resulting products in the merged plumes were collected using a glass separation funnel for 10 min. Exhaust gas was pumped out from the bottom, while glass wool was used to cover the gas outlet, avoiding loss of products. The distance and angle between the two microdroplet spray emitters influenced the formation of products, as described later. The reaction mixture was extracted with EtOAc and analyzed by gas chromatography (GC). The product 4-Nitrobenzaldehyde (**2**) was detected by GC in 72% yield, as shown in Figure 1b. Other materials such as aluminum foil and Teflon were also investigated as collection surfaces, with no apparent difference in product formation (Supporting Information, Figure S1). This observation indicated that the reactions were not mediated by the collection surface. The travel distance of the microdroplets determined the degree of product conversion in previously reported reactions.[12a] We changed the distance between the spray emitters and collection surface from 5 to 10 cm and did not find a change in product yield (Supporting Information, Figure S2), which shows the fast reaction occurred in the microdroplets before they landed on the surface. Compressed air and helium gas were also tried as the sheath gas with no apparent changes in the yields (Supporting Information, Figure S3). Three control experiments were performed in bulk (Figure 1c), drop-casted millimeter-size droplets (Figure 1d), and droplets generated using a 29 nL micro-T-junction (Figure 1e) with reaction times of 10 min or more (see Supporting Information for details). GC confirmed that no reaction occurred under any of these three conditions (Figure 1f). A previous study also showed that no oxidation occurred in the absence of the phase-transfer catalyst in bulk solution.[17b]

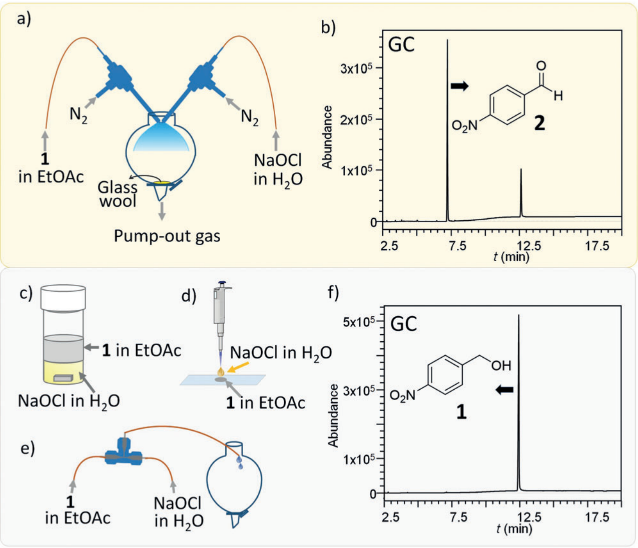


Figure 1. a) Two-phase oxidation reaction between 4-nitrobenzyl alcohol (**1**) with NaOCl performed in microdroplets generated by the atomization of respective bulk solutions with a turbulent nebulizing gas (dry N_2) at 120 psi; b) gas chromatogram of a two-phase oxidation reaction under (a) conditions showing the formation of the product 4-nitrobenzyladehye (**2**) in 72% yield. c) Two-phase reagents were mixed in bulk and stirred vigorously for 10 min. d) Millimeter-size droplets of the two reagents were drop-casted on top of each other. e) Two streams of droplets were mixed in a micro-T-junction and then directed to a collection funnel. f) Gas chromatogram of two-phase oxidation reaction under the conditions shown in (c). Similar traces were obtained under the conditions shown in (d) and (e). GC yields were determined using standard curves generated from a series of known standards referenced to the internal standard benzaldehyde.

The sharp contrast between the two-phase reaction behavior in microdroplets from that in the bulk and large droplets (100 μm to 5 mm) emphasized the importance of droplet size (surface-to-volume ratio) in driving the two-phase reactions. With a decrease of the droplet size from mm to micrometer, the surface-to-volume ratio increases three orders of magnitude.[15] We decreased the size of the droplets by either fixing the pressure of the sheath gas and using capillaries with inner diameters (i.d.) of 50, 100, and 250 μm (outer diameter of 360 μm) to generate microdroplets with different initial sizes; or fixing the diameter of the capillary and changing the sheath gas pressure from 50 to 150 psi (1 psi = 6894.76 Pa) to decrease the droplet size by increasing the shearing force (Supporting Information, Figure S4). Slightly increased product formation was observed for a capillary of 50 μm i.d. and under 150 psi (Supporting Information, Figure S5). This suggests that below a certain droplet diameter, further decrease of droplet size has no significant effect on the two-phase reactions.

To explore other intrinsic factors that facilitate the liquid–liquid reaction in microdroplets, different methods of generating microdroplets and ways of interacting between the two-phase droplets were investigated. In Figure 2a, a fused silica capillary fed with **1** in EtOAc was inserted into a concentric capillary fed with NaOCl aqueous solution to produce an annular flow. The bottom of the inner capillary was first kept at the same level with that of the outer capillary. Two phases came into contact only when they entered the tip of the spray emitter. GC shows that a yield of 18% (Figure 2g) was obtained. When we set the inner capillary back to the outer concentric capillary (Figure 2b), a better yield (27%) resulted. To further increase the contact time of the two phases, we mixed them by cross flow in a micro-T-junction and kept the droplet segments flowing through a length of capillary followed by spraying of the droplets onto the surface (Figure 2c). Fairly good conversion from **1** to the product was obtained in some trials. However, the yield varied (from 30–58%) in different batches. Possible reasons for the unsteady formation of the products might be related to

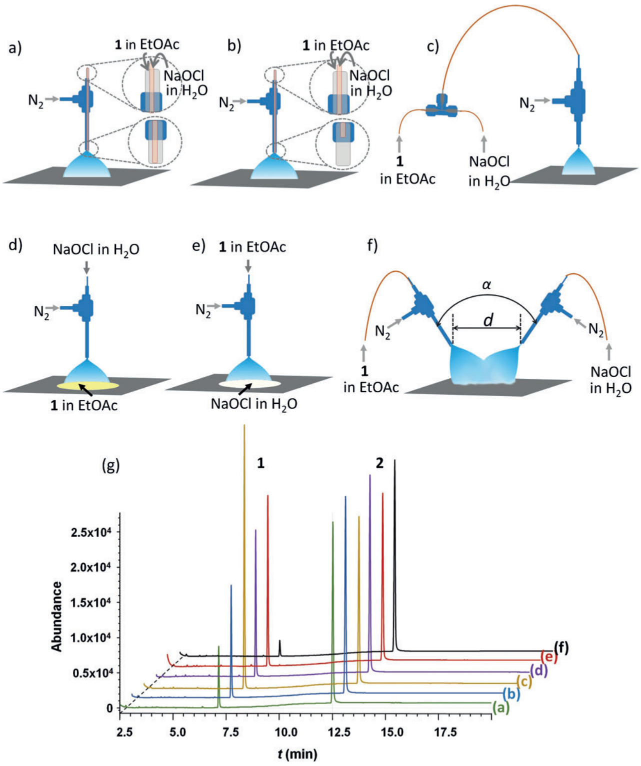


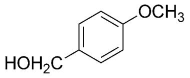
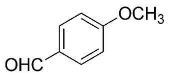
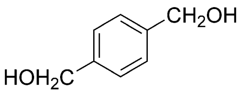
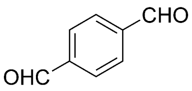
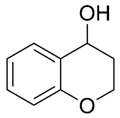
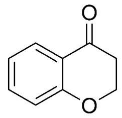
Figure 2. a) Two-phase annular flow was generated by inserting the capillary tube fed with **1** in EtOAC into the capillary tube fed with aqueous NaOCl and nebulized by sheath gas. The bottom of the inner capillary was first kept at the same level with that of the outer capillary. b) Inner capillary was set back to the outer concentric capillary. c) Two-phase cross flow was formed by mixing **1** and NaOCl in a micro-T-junction and sprayed. d) Microdroplets of **1** in EtOAc were sprayed onto the collection surface followed by spraying NaOCl in water onto the layer of **1**. e) Microdroplets of aqueous NaOCl were sprayed onto the collection surface followed by spraying **1** in EtOAc onto the layer of NaOCl. f) Dual spray of **1** in EtOAc and aqueous NaOCl at distance *d* and angle *α* onto the collection surface. g) Gas chromatogram of two-phase oxidation reaction under the conditions in (a, green; b, blue; c, yellow; d, purple; e, red; and f, black).

the effect of the high-pressure sheath gas on mixing two-phase droplets before and after their exiting the capillary. More studies are ongoing for this device, while a key clue obtained here was that NaOCl did not come in contact effectively with **1** when it was in the microdroplets in the low yield batches. To verify this hypothesis, we divided the microdroplet reaction into two types: 1) Microdroplets of **1** in EtOAc were deposited onto the surface followed by spraying aqueous NaOCl onto the layer of **1** (Figure 2d) or 2) vice versa (Figure 2e). GC analysis showed repeatable product conversions for both setups, although the yields were relatively low (33% and 38%, respectively). This behavior was caused by the fact that the interfacial area of one reagent on the collection surface was not fully used to interact with the other and droplets were partially fused upon their deposition onto the surface.

Therefore, we forced microdroplets of the two phases to collide with each other in a Y-shape intersection without touching any other surface before they were collected (Figure 2f). Note that both of the two-phase spray plumes were initiated by sheath gas instead of either one or both being initiated by an electric field as in the extractive electrospray[18] or microdroplet fusion[12b] experiments. There is a thin intervening gas film between the surfaces of two droplets. If the collision kinetic energy (mainly gained from sheath gas) of the two droplets is not sufficient to penetrate this gas layer, the droplets bounce off each other, resulting in no physical contact between two liquid droplets.[19] This behavior can be seen from the gas chromatograms obtained when the distance between two spray emitters (*d*) exceeded 80 mm. Almost no product was formed in such microdroplet reactions. The optimized distance *d* of 1.5 mm with an angle *α* of 80° between two spray emitters pointing to the surface enabled effective collisions (coalescence, disruption, or/and fragmentation[19]) between microdroplets to occur. A representative gas chromatogram obtained under this configuration is shown in Figure 1b with an overall product yield of 72%.

Encouraged by these results, we further examined the microdroplet two-phase oxidations of several other alcohols including benzyl alcohols with different substituents, 1,4-benzenedimethanol and secondary alcohol as shown in Table 1. In all cases tested, the desired oxidation products of individual alcohols were obtained without using phase-transfer catalysts in moderate to good yields.

Table 1: Oxidation of various alcohols in two-phase microdroplets.

Reagent[a]	Product	Yield [%]
		64
		75
		52

[a] 1,4-Benzenedimethanol has poor solubility in EtOAc. Its oxidation was performed in acetonitrile, which still formed two phases when mixed with aqueous NaOCl (12.5%).

To demonstrate the practical utility of the present two-phase microdroplet synthesis method, a preparative-scale experiment was performed. Four pairs of dual microdroplet sprayers were arranged radially and converged at the tips of spray emitters (Figure 3). Two-phase liquids were introduced through the five-port mixers to the spray emitters. Sheath gas (N_2) was delivered using two gas manifold systems. Accordingly, a rate of 1.2 $mg\,min^{-1}$ was realized for the synthesis of 4-nitrobenzylaldehyde (**2**) with an isolated yield of 64%. Its ^1H-NMR spectrum is provided after purification (Supporting Information, Figure S5).

In summary, we have demonstrated that two-phase reactions can be carried out in microdroplets rapidly and with good yields without using phase-transfer catalysts. Various alcohols including primary and secondary alcohols were oxidized to their corresponding aldehydes and ketones.

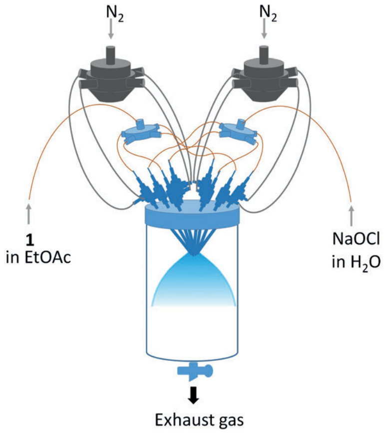


Figure 3. Scale-up of two-phase microdroplet oxidation of **1** in EtOAc (0.2 M) with aqueous NaOCl (12.5 %) by four pairs of dual microdroplet spray systems.

Microdroplets generated by six methods showed different efficiencies for two-phase reactions. Our results indicate that not only the increased interfacial areas but also effective communications between the microdroplets of the two phases play a crucial role in facilitating the two-phase reactions in the absence of phase-transfer catalysts. A preparative-scale experiment was also performed and yielded product at an isolated rate of 1.2 mg min^{-1}, which demonstrates the possible practical utility of the present method.

Experimental Section

For the two-phase microdroplet synthesis of 4-nitrobenzaldehyde (**2**), 4-nitrobenzyl alcohol (**1**, 0.2 M) in ethyl acetate and aqueous sodium hypochlorite (12.5 %) were loaded at equal volume into two airtight glass syringes and were delivered with a syringe pump (Harvard Apparatus) at a flow rate of 15 μL min^{-1} to two separate capillaries with an i.d. of 100 μm and o.d. of 360 μm. The ends of the capillaries were equipped with two sheath-gas-assisted spray emitters. The angle between the two spray sources was set between 60° and 80°. The distance between the two capillaries was set in a range of 0.5–2 mm, depending on the angle of the two spray sources. The dry N$_2$ gas, which served as the sheath gas, was operated at 120 psi. A glass surface was used to collect the merged plumes from two spray sources. Upon completion of the reaction, ethyl acetate was used to extract the product from water and the product was dried by sodium sulfite. The product yield was determined by GC. For further information on the instrument, see the Supporting Information.

Acknowledgements

We thank Katherine Walker who made available to us the GC instrument in the Waymouth laboratory. H. C. appreciates the financial support from the China Scholarship Council (201508330736) and the National Natural Science Foundation of China under project No. 21405030. This work was supported by the Air Force Office of Scientific Research through Basic Research Initiative grant (AFOSR FA9550-16-1-0113).

Conflict of interest

The authors declare no conflict of interest.

Keywords: liquid–liquid reactions · microdroplet synthesis · phase-transfer catalysis · Stevens oxidation · two-phase reactions

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Manuscript received: December 19, 2016
Revised: February 6, 2017
Final Article published: ■■ ■■, ■■■■

Communications

Synthetic Methods

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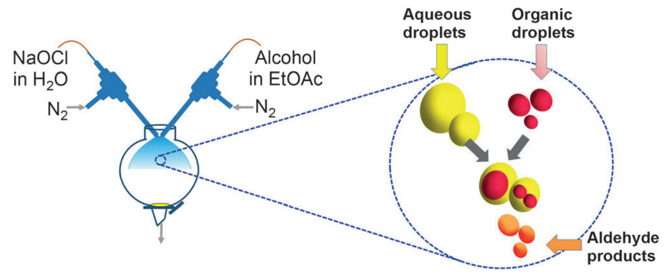
Two-Phase Reactions in Microdroplets without the Use of Phase-Transfer Catalysts



It's all about the interface: Biphasic reactions are carried out in microdroplets without using a phase-transfer catalyst. Reactions occur within milliseconds in moderate to good yields.