

DROPLET REACTORS WITH CATALYTIC INTERFACES: AN ACTIVE FLUOROUS PHASE FOR SEGMENTED-FLOW MICROFLUIDIC REACTIONS

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ABSTRACT

By combining droplet-based microfluidics with fluoruous biphasic catalysis, we generated droplet reactors with catalytically active walls and used these compartments as a tool for organic synthesis. Our approach provides a closed-loop system for catalyst recycling, controlled catalytic reaction compartments, and the opportunity for facile on-line optimization.

KEYWORDS: Microdroplets, Fluorous biphasic catalysis, Green chemistry, Suzuki-Miyaura coupling

INTRODUCTION

We have developed a method for biphasic catalysis that incorporates the efficiency and control of droplet-based microfluidics [1,2] with emerging fluoruous phase chemistry [3]. Using a microfluidic system, we generated discrete droplet reactors with catalytically active interfaces and used these compartments to conduct palladium-catalyzed Suzuki-Miyaura reactions. In the drive towards miniaturizing and automating chemistry, droplet-based microfluidics has emerged as a powerful research platform [1,2]. In many applications, the continuous phase serves merely to physically separate the droplets from each other without playing an active role in the chemical reaction. Other applications have involved biphasic reactions facilitated by transfer of reagents between the dispersed and continuous phases [1,2]. We aimed to use the multiphase nature of microdroplets to facilitate biphasic catalytic reactions. We envisioned anchoring a catalyst in the carrier phase such that it could assemble at the droplet ‘wall,’ catalyzing reactions inside each droplet. In order to achieve this we used a fluoruous continuous phase, which provided an environment orthogonal to conventional organic and aqueous chemistry.

EXPERIMENTAL

Reactions were performed in 750 μm ID PTFE tubing using an aqueous solution of K_2CO_3 (136 mM), arylboronic acid (55 mM), and aryl halide (45 mM) and a solution of catalyst (0.136 mM $\text{Pd}(\text{OAc})_2$, 0.272 mM **1**) in FC-77 with fluoruous/aqueous flow rates of 690/414 $\mu\text{l/h}$ (319/96 $\mu\text{l/h}$ for Table 1, Entry 5). Synthesis of fluoruous ligand **1** was adapted from Li *et al* [4].

RESULTS AND DISCUSSION

Using a T-junction, monodisperse aqueous droplets containing Suzuki-Miyaura substrates were formed within a fluororous continuous phase containing the palladium catalyst, resulting in controlled catalytic interfaces (Figure 1). In order to solubilize the catalyst in the fluororous phase and to position the catalyst at the droplet interface, we designed and synthesized an amphiphilic ligand (**1**) containing a fluorinated tail and a hydrophilic guanidine head as shown in Figure 1a. The reaction proceeded as the droplets

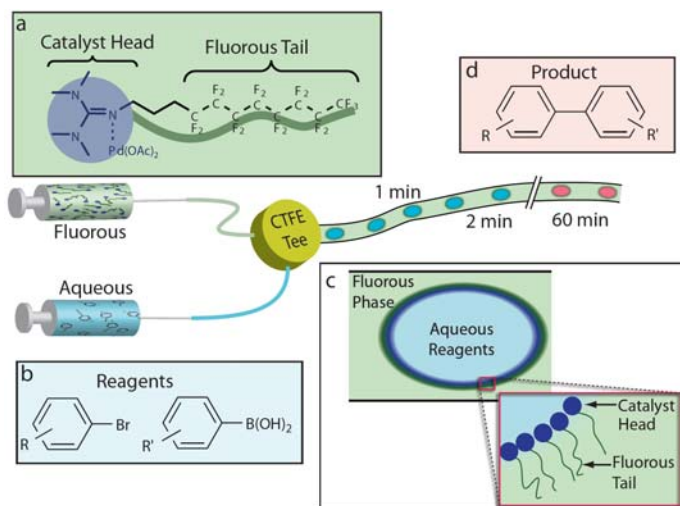


Figure 1. Illustration of microdroplets with catalytically active interfaces

Table 1. Fluororous biphasic Suzuki-Miyaura couplings in droplets

$\text{R-Br} + (\text{HO})_2\text{B-R}' \xrightarrow[\text{Pd(OAc)}_2, \text{1, FC-77, rt}]{\text{K}_2\text{CO}_3, \text{H}_2\text{O}} \text{R-R}'$				
Entry	R-Br	(OH) ₂ B-R'	Residence time (h)	Yield (%)
1			3	90
2			3	77
3			0.75	99
4			1	91
5			8	63

flowed from the T-junction through the reaction channel, affording an array of products from both activated and deactivated aryl bromides in good yield at room temperature as shown in Table 1.

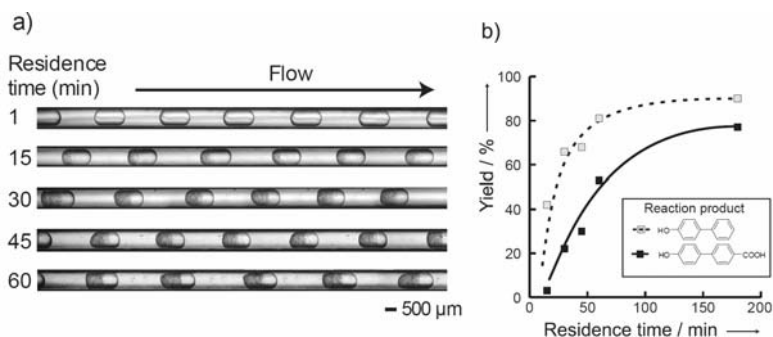


Figure 2. Reaction kinetics followed visually (a) and by HPLC (b)

Using this setup it is possible to dial in a variety of different parameters, providing a means for online reaction optimization. In many cases, the product precipitates (Figure 2a), providing an immediate visual signal for the reaction progress which was used to adjust reaction conditions in real time to improve yield. For further optimization, samples were quenched and analyzed by HPLC offline to quantify product formation (Figure 2b). We further exploited the continuous nature of this system by showing that the catalytically active fluoros phase could be recycled in a uninterrupted closed-loop. Droplets were pooled at the end of the reaction channel, the aqueous and fluoros phases separated by density, and the fluoros phase was pumped back into the droplet formation module to catalyze further reactions in the next cycle. This green chemistry approach ‘closes the loop’ to prevent waste.

CONCLUSIONS

Our work demonstrates the use of droplet-based microfluidics to create controlled catalytic interfaces for organic synthesis in flow. We have also developed green conditions for the widely used Suzuki-Miyaura reaction by synthesizing a novel fluoros guanidine ligand that facilitates Suzuki couplings under fluoros-aqueous biphasic conditions without the addition of an organic co-solvent. Furthermore the reaction proceeds under mild, room temperature conditions making it particularly attractive for late-stage coupling applications that could benefit from microfluidic efficiency and minimal reagent consumption.

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