

# Palladium-Catalyzed Carbon–Carbon Cross-Coupling Reactions in Thermomorphous Double Emulsions

Viktor Misuk<sup>1\*</sup>, Andreas Mai<sup>1</sup>, Konstantinos Giannopoulos<sup>1</sup>, Dominik Karl<sup>1,2</sup>, Julian Heinrich<sup>1</sup>, Daniel Rauber<sup>1</sup> and Holger Löwe<sup>1,2\*</sup>

<sup>1</sup>Johannes Gutenberg University Mainz, Duesbergweg 10–14, D-55128, Mainz, Germany

<sup>2</sup>Fraunhofer ICT-IMM, Carl-Zeiss-Str. 18–20, 55129, Mainz, Germany

Received: 25 November 2014; accepted: 09 December 2014

The method of combining the concept of fluoruous biphasic catalysis (FCB) with micro multiple emulsions benefits from the advantages of homogeneous as well as from heterogeneous catalysis in continuous micro flow. In this particular case, three immiscible fluid phases in continuous micro segmented flow were used to perform palladium-catalyzed Heck cross-coupling reactions of styrene with aryl halides. A capillary tube-in-tube coaxial flow setup in combination with a glass micro reactor was used to produce monodisperse aqueous phase/organic phase/perfluorinated phase double emulsions. The resulting emulsions had a core–shell droplet structure composed of a perfluorocarbon fluid in which a palladium catalyst with fluorinated phosphine ligands was dissolved, an organic phase consisting of a solvent and two reagents, and an alkaline aqueous solution. The fluoruous and organic phases of the double emulsion form a thermomorphous system which can be converted into one phase by an increase of temperature above 150 °C, and the catalytic reaction is performed temporarily. By decreasing the temperature, a phase separation takes place; after that, the organic phase contains the product and the catalyst is located in the fluoruous phase. The separated catalyst solution was reused several times without a noticeable loss of activity. The main advantage of this method is to use temporarily very high catalyst concentrations in each droplet, while employing only small amounts of the catalyst for the overall reaction volume.

**Keywords:** Heck coupling, double emulsion, thermomorphous solvent, chlorobenzene, bromobenzene

## 1. Introduction

Nowadays, a wide variety of important reactions is catalyzed by transition metals. The palladium-catalyzed cross-coupling of olefins with aryl or vinyl halides, known as the Heck reaction, is a well-known example for forming carbon–carbon bonds or introducing functional groups into substrate molecules. The Heck reaction has found applications in the preparation of a wide spectrum of organic chemicals, materials, and natural products [1–4].

The Heck coupling reaction can be carried out homogeneously or heterogeneously. Most of the reactions are performed in homogeneous systems including the catalysts, reactants, and products in one phase. In these systems, mild reaction conditions are applied. The activity and selectivity of the catalytic species are remarkably good, whereas it is difficult to separate the catalyst from the product. This common disadvantage makes it practically impossible to reuse the catalyst. When using heterogeneous reaction conditions, the catalyst can be recycled, but the catalyst activity is, in comparison to homogeneous systems, significantly lower [5–7].

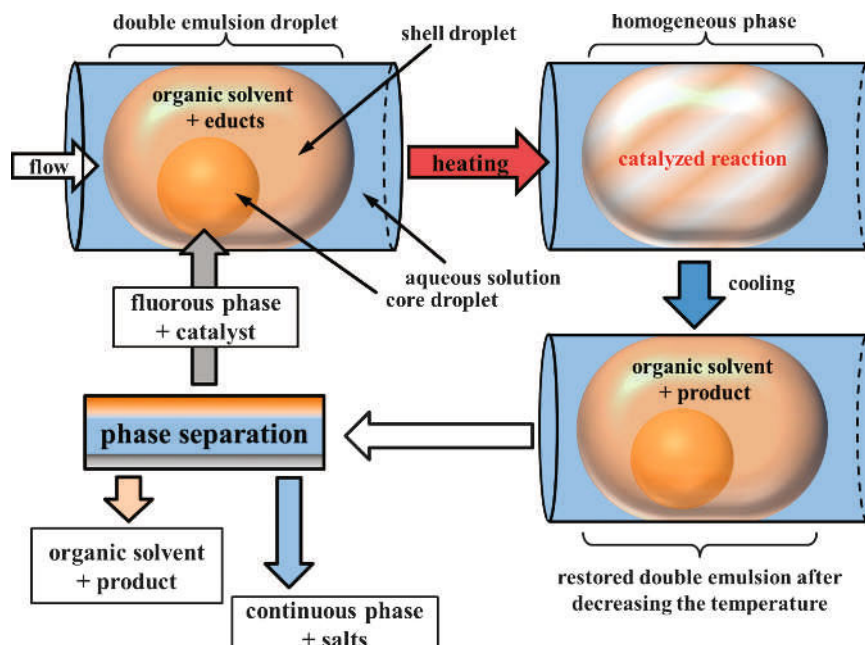
The fluoruous biphasic catalysis (FBC) concept makes it possible to combine the advantages of both, the homogeneous with the heterogeneous procedures. This is achieved by using two different liquid phases, an organic phase, and a perfluorinated phase [8, 9]. The temperature-dependent miscibility of perfluorinated liquids with common organic solvents allows the establishment of a system in which the catalytic reaction takes place in a homogeneous phase at higher temperatures and where the catalyst separation occurs in a heterogeneous system at lower temperatures [10–14]. The catalyst must exhibit perfluorinated ligands, making it preferably soluble in the perfluorinated phase.

In this paper, the combination of the FBC concept and multiphase micro flow is introduced. The usage of droplet-based microfluidics for chemical synthesis allows the performance

of chemical reactions on a micro scale under well-defined conditions. One of the most significant advantages of droplet-based systems is the accurate control of residence time of the reagents in the reactor [15–17]. In comparison to single phase microfluidics, the encapsulation of reagents within droplets eliminates their dispersion due to convection and diffusion along the flow pathway. To control the residence time in a system containing three different phases, double emulsions can be used. Double emulsion droplets make it possible to bundle multiple phases in any chosen composition according to the desired stoichiometric ratio. The resulting double emulsion droplets allow the performance of multiphase reactions where each double emulsion droplet can be assumed to be an isolated reactor. In the present work, palladium-catalyzed Heck cross-coupling reactions of styrene with different aryl halides were performed in multiphase micro flow. In contrast to common FBC which uses two reactive phases, the system used in this work consists of three phases. A capillary tube-in-tube coaxial flow setup in combination with a glass micro reactor was used to produce monodisperse aqueous phase/organic phase/perfluorinated phase double emulsions. The resulting emulsions had a core–shell droplet structure with an organic shell (outer droplet) and fluorinated core (inner droplet). The core–shell droplets were dispersed in a continuous aqueous phase (Figure 1).

The three different phases were composed of: (1) a perfluorocarbon fluid in which a palladium catalyst with fluorinated phosphine ligands was dissolved; (2) an organic phase consisting of a solvent, styrene, and an aryl halide; and (3) an alkaline aqueous solution. The fluoruous and organic phases of the double emulsion compose a thermomorphous system and can be converted into one homogeneous phase through an increase of temperature above 150 °C. In the homogenous one-phase state, the palladium catalyst comes in contact with the organic reactants, and thus, a homogenous catalyst reaction is performed. The time-determining step of the reaction takes place in the homogeneous solution, while the last step of the catalytic cycle, the reductive elimination, takes place on the surface between the dispersed and the

\* Authors for correspondence: misukv@uni-mainz.de (V.M.) and loewe@uni-mainz.de (H.L.)



**Figure 1.** Schematic illustration of the coupling reaction performed in thermomorphous double emulsions followed by a phase separation step. The composition of the double emulsion is: core droplet=FC-40®+catalyst, shell droplet=solution of aryl halide and styrene in toluene, and continuous phase=solution of  $K_2CO_3$  in water. The flow direction is from left to right

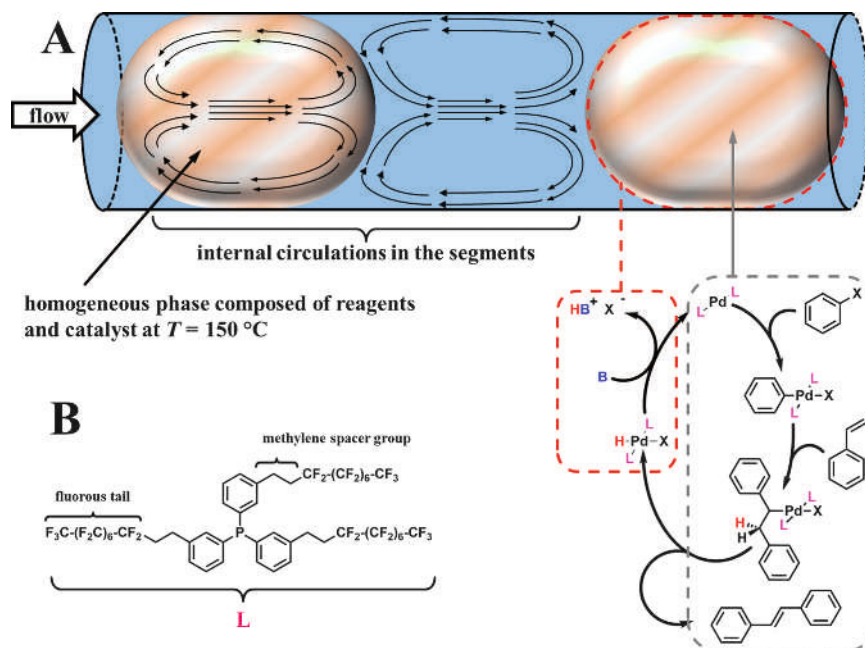
continuous phase. By decreasing the temperature of the system, a phase separation takes place and the core–shell structure is restored. Again, only the core droplet contains the catalyst, and the product is located in the shell droplet (see Figure 2).

## 2. Results and Discussion

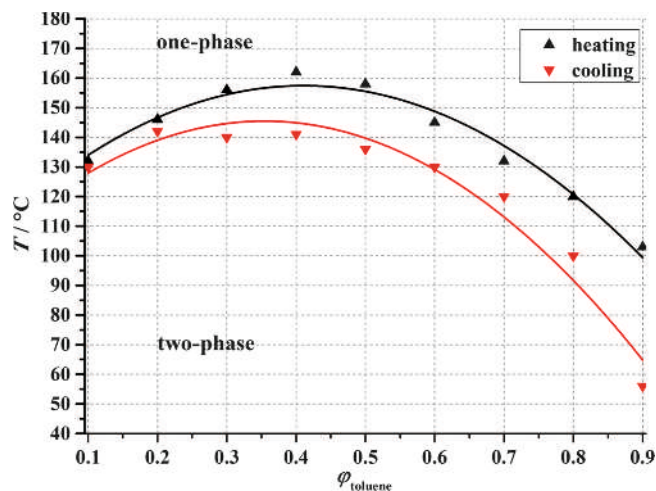
Based on the temperature-dependent miscibility of the per-fluorinated solvent, Fluorinert FC40®, with toluene, thermomorphous double droplets were generated in a capillary-based microreactor. Given that the different phases are immiscible below a certain temperature and, in consequence, the catalytic reaction does not take place, it is necessary to primarily determine

the operation range in order to purposefully utilize the phase switch property. In order to obtain exact data concerning the temperature-dependent miscibility, a phase diagram of the system FC 40–toluene for different compositions was determined. The phase diagram for the pure solvents is shown in Figure 3. The solutions used in the experiments contain reactants and, thus, diverge slightly from the determined phase diagram. The temperature above which the two solutions are miscible is always 8–10 °C lower compared to the mixture of the pure solvents.

By using identical flow rates for the perfluorinated phase (core droplet) containing the precatalyst  $L_2PdCl_2$  ( $L$ =[tris(3-(1H,1H,2H,2H-perfluorodecyl)-phenyl)-phosphine]) and for the organic shell droplet containing the reactants, the resulting double



**Figure 2.** A, Illustration of the reaction performed. The flow direction is from left to right. The grey dotted line marks the steps (oxidative addition, insertion, and  $\beta$ -hydride elimination) which occur within the droplet after it becomes homogeneous. The red dotted line marks the reductive elimination step which occurs at the aqueous–organic interface. The internal circulations in the segments accelerate the interfacial reaction. B, Structure of the fluororous ligand used for the reactions. Ligands of this type ensure that the catalytic active species are preferably soluble in the perfluorinated phase



**Figure 3.** Thermomorphous behavior of the binary system consisting of toluene and Fluorinert FC40. At low temperatures, two separate phases exist. By an increase of temperature, the two phases combine into one. This process is reversible by lowering the temperature. The miscibility tests were carried out in a pressurized, stirred glass flask. Given amounts of toluene were added to FC 40 and heated in an oil bath until the mixture became homogeneous. Then, the oil bath was slowly cooled down until the phase separation occurred

emulsion droplets had a ratio of  $\phi_{\text{fluorous}}=0.5$  and a mixing temperature of 149 °C.

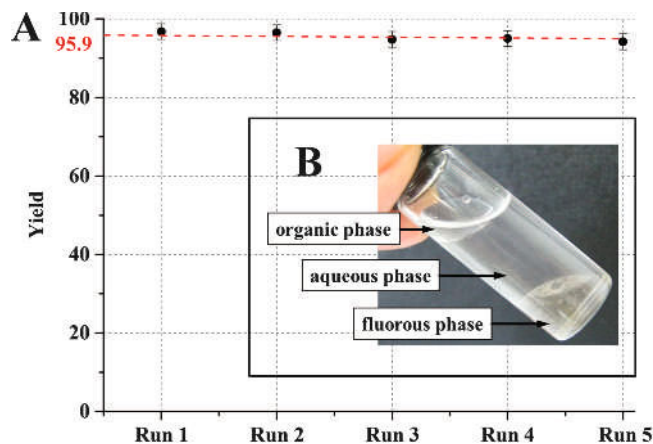
Two catalyst solutions, with 1.54 and 9.25 mol% (referred to the aryl halide) respectively, were used in the experiments.

To test reactants with different order of reactivity, palladium-catalyzed cross-coupling of bromobenzene and chlorobenzene with styrene were performed as model reactions. The effects of different reaction parameters, including residence time of the thermomorphous double emulsion droplets in the reactor, temperature, and catalyst concentration, for the coupling reaction are listed in Table 1.

In the case of bromobenzene, while using 1.5 mol% of the catalyst, essentially, no product was detected at 100 °C. The double emulsion remained intact at these conditions, and only traces of the catalyst were dissolved in the organic phase (according to Figure 4). By raising the temperature to 150 °C, homogenization was achieved and the desired coupling product (trans-stilbene) was collected with a 96% yield after a residence time of 18 min. Analogue cross-coupling reactions in stirred batch reactors under standard conditions take roughly 5 h to achieve comparable yields. Subsequently, with a simple phase separation procedure, the three phases, i.e., aqueous alkaline-, organic-, and catalyst-containing phase were separated. When chlorobenzene and 1.5 mol% catalyst were used, only 33% of the coupling product was observed, even after an extended reaction time of ~1 h. At significantly higher catalyst concentrations (9 mol%), a yield of 78% was achieved in the same reaction time (~1 h). To demonstrate the catalyst recycling, the reaction of bromobenzene with styrene was repeated several times. The catalyst solution was reused after each cycle without any purification. The catalytic activity did not significantly decline, even after repeating the experiment five times. The yields of the first five runs did not change, and they are shown in Figure 4. In the sixth run, the yield, however, suddenly declined to 40%. Also, no precipitation of particles was visible, but the

**Table 1.** Palladium-catalyzed cross-coupling of aryl halide with styrene

X	$c_{\text{cat}}$ (mol%)	T (°C)	$\tau$ (min)	p (bar)	Yield (%)
Br	1.54	100	18	5.4	<1
Br	1.54	150	18	5.4	96
Cl	1.54	150	23	5.4	15
Cl	1.54	150	56	5.4	33
Cl	9.25	150	14	5.4	32
Cl	9.25	150	56	5.4	78



**Figure 4.** A, Yield of the desired coupling by reusing the catalyst solution five times. After the fifth run, a significant drop in yields took place (40%). B, Photograph of the collected triphasic sample

perfluorinated solution became darker run by run which indicates the formation of Palladium black. The drop in catalytic activity occurs most likely due to the disproportionation of the active  $14 e^-$  — PdL<sub>2</sub> complex to a stable PdL<sub>3</sub> and an instable PdL complex. The latter aggregates to clusters, which account for the discoloration of the fluorous phase [18].

### 3. Conclusions

A microchannel reactor provides an attractive alternative to common stirred batch flasks. Fast transfer of heat and mass, and high surface-to-volume ratios are the benefits of the miniaturization. The performing of coupling reactions in thermomorphous microscale double emulsion allows an increase in the catalytic efficiency, a significantly decrease of the reaction time and a reduction of the number of postreaction purification steps. Furthermore, the composition of the double emulsion droplets and, thus, exact stoichiometry can be controlled easily by the flow rates of the three phases. The resulting droplet-flow regime, where isolated liquid slugs move along the channel, make it possible to control the reaction time precisely. In addition, the presence of interfaces in the channel causes counter-rotating recirculation zones inside and outside of the droplet, which enhance the mass transport, and accelerate the reactivation of the catalyst through the reductive elimination step.

The application of thermomorphous double emulsions enables fast cross-coupling reactions with reusable catalyst solutions. Once prepared, a small volume of highly concentrated catalyst solution can be used to convert its volume of the substrate solution several times. A conventional batch process with the same total substrate volume would have a much lower relative catalyst concentration (unit=mol%) if the same absolute catalyst amount (unit=mol) was used. Hence, to employ the same relative concentration, much higher absolute amounts of the catalyst would be necessary.

Inserting the catalyst solution into the shell droplets leads to a very high local catalyst concentration, which speeds up reactions considerably (compare Figure 1). Even less active substrates, e.g., chlorobenzenes, can be converted in a much shorter time.

Because the phase separation occurs readily when the reaction mixture is cooled, the catalyst can be recovered easily without the need for time- and resource-consuming workup steps. Therefore, the benefits of high catalyst amounts can be used in the double emulsion droplet flow, while the same conditions would be prohibitively expensive in batch processes.

Automation of the double emulsion process can be achieved by employing a continuously performing microseparation module. After the performed reaction, the catalyst solution can be



separated automatically from the reaction mixture and fed back to a reservoir. The organic and aqueous phases can also be separated in the same manner.

To improve the efficiency of the catalyst recycling, it is necessary to increase the limited stability of the catalyst–ligand complex. Further work on perfluorinated ligands, which suppress disproportionation and prevent Pd-black formation, is now in progress.

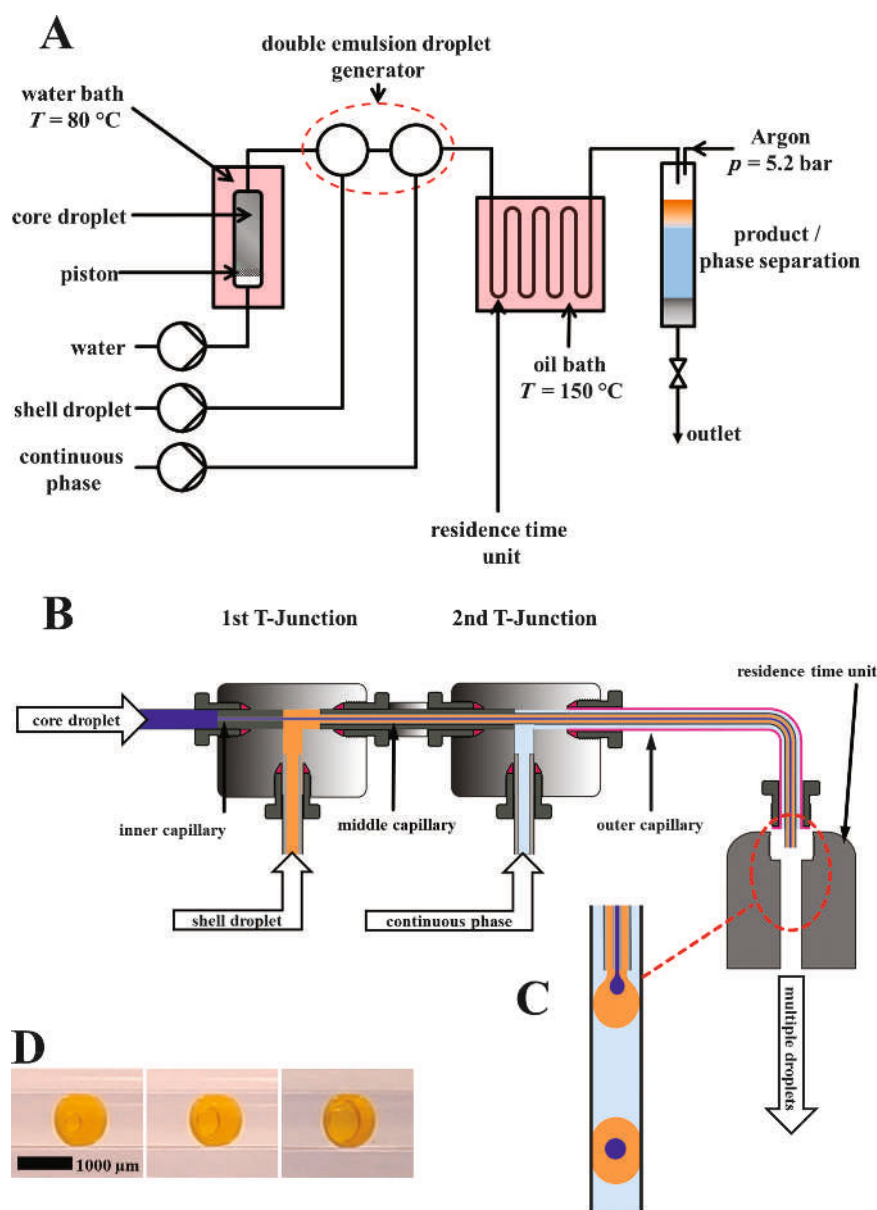
## 4. Experimental

**4.1. Chemicals and General Procedures.** All reagents were purchased from Sigma-Aldrich. Bromobenzene, chlorobenzene, and toluene were distilled immediately prior using. Three solutions were used to perform the reactions: (1) organic phase containing aryl halide ( $c=0.032$  mol/L) and styrene ( $c=0.036$  mol/L) in toluene; (2) perfluorinated phase composed of Pd-catalyst [bis[tris(3-(1*H*,1*H*,2*H*,2*H*-perfluorodecyl)-phenyl)-phosphine]palladium(II)-dichloride],  $c=4.93 \times 10^{-4}$  mol/L or  $c=2.96 \times 10^{-3}$  mol/L

L dissolved in Fluorinert FC40®; and (3) aqueous phase with  $K_2CO_3$ ,  $c=0.088$  mol/L.

Preparation of the catalyst solution was carried out by using standard Schlenk techniques. Gas chromatography measurements were carried out with Varian GC 3900. Yields of the coupling product were determined versus an internal standard (biphenyl).

**4.2. Continuous-Flow Experiments.** All continuous-flow cross-coupling reactions in double emulsions were performed using a modular flow reactor as shown in Figure 5A. For the fluid delivery, a Fraunhofer ICT-IMM syringe pump system was used in combination with stainless steel syringes. To ensure that each double emulsion droplet has the same amount of catalyst, the solution of the catalyst and FC-40® which is cloudy at room temperature was preheated to a temperature of above 60 °C at which it became clear. The catalyst solution was pushed in the double emulsion droplet generator by a piston which is driven by an additional water pump.



**Figure 5.** A, Schematic illustration of the flow reactor used to perform coupling reaction in thermomorphous double emulsions followed by a phase separation step. B, Setup of the double emulsion droplet generator in detail. Composition of the double emulsion is: core droplet=FC-40+catalyst, shell droplet=solution of aryl halide and styrene in toluene, and continuous phase=solution of  $K_2CO_3$  in water. C, Formation of emulsion droplets in the resulting coaxial configuration of the capillaries. D) Microscope images of resulting double emulsions. The amount of perfluorinated phase can be easily adjusted by varying the flow rates. The organic phase is colored yellow for better visibility. The ratios between the fluorinated phase and organic phase are (from left to right) 1:10, 1:5, and 1:1

The unit for the processing of double emulsion droplets (Figure 5B–D) is constructed as a modular capillary tube-in-tube microreactor consisting of two stainless steel T-junctions with 1000  $\mu\text{m}$  inner diameter borings and three different capillary tubings (core capillary, PEEK, with an outer diameter [OD]=360  $\mu\text{m}$  and an inner diameter [ID]=150  $\mu\text{m}$ . Middle capillary, FEP, OD=1/32", ID=500  $\mu\text{m}$ . Outer capillary, PTFE, OD=1/16", ID=1,000  $\mu\text{m}$ ).

The used residence time unit is a glass device with a round channel, inner volume of 1.7 mL, and an inner diameter of 1000  $\mu\text{m}$ , commercially available through Little Things Factory GmbH. A pressure stable glass column (Omnifit) was used for sample collection. A back pressure of  $p=5.4$  bar was applied on the whole system to avoid evaporation of the solvents. The organic and aqueous solutions were loaded into syringes and the catalyst solution into a preheating unit. The pressure was applied through an argon gas bottle. By injecting the immiscible fluids in the capillaries, a continuous uniform flow of monodisperse double-emulsion droplets was formed. Due to the absence of surfactants, the resulting double emulsion droplet dimensions depended strictly on the inner diameter of the reactor channel and the applied flow velocities. By passing through the heated residence time unit ( $T=150$  °C), the double emulsions subsequently become homogeneous and the reaction takes place, while in the collecting tube, a complete phase separation occurs.

After the reaction, the collected sample was cooled down to 5 °C for several hours to ensure complete phase separation and avoid catalyst leaching in the organic phase. Then, the alkaline solution

was discarded, the organic phase was analyzed by gas chromatography, and the fluoruous phase, containing the catalyst, was reused without further treatment.

## References

1. Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320–2322.
2. Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066.
3. de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed.* **1995**, *33*, 2379–2411.
4. Danishefsky, S. J.; Masters, J. J.; Young, W. B.; Link, J. T.; Snyder, L. B.; Magee, T. V.; Jung, D. K.; Isaacs, R. C. A.; Bornmann, W. G.; Alaimo, C. A.; Coburn, C. A.; Di Grandi, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 2843–2859.
5. Ramchandani, R. K.; Vinod, M. P.; Wakharkar, R. D.; Choudhary, V. R.; Sudalai, A. *Chem. Comm.* **1997**, 1997, 2071–2072.
6. Djakovitch, L.; Koehler, K. *J. Am. Chem. Soc.* **2001**, *123*, 5990–5999.
7. Molnar, A.; Papp, A.; Miklos, K.; Forgo, P. *Chem. Comm.* **2003**, 49, 2626–2627.
8. Horvath, I. T.; Rabai, J. *Science* **1994**, *266*, 72–75.
9. Behr, A.; Henze, G.; Johnen, L.; Awungacha, C. *J. Mol. Catal.* **2008**, *285*, 20–28.
10. Schneider, S.; Bannwarth, W. *Angew. Chem.* **2000**, *39*, 4142–4145.
11. Lu, N.; Lin, Y.-C.; Chen, J.-Y.; Fan, C.-W.; Liu, L.-K. *Tetrahedron* **2007**, *63*, 2019–2023.
12. Lu, N.; Lin, Y.-C.; Chen, J.-Y.; Fan, C.-W.; Liu, L.-K. *Tetrahedron Lett.* **2008**, *49*, 371–375.
13. Li, C.-K.; Ghalwadkar, A.; Lu, N. *J. Organomet. Chem.* **2011**, *696*, 3637–3642.
14. Rocaboy, C.; Gladysz, J. A. *New J. Chem.* **2003**, *27*, 39–49.
15. Song, H.; Tice, J. D.; Ismagilov, R. F. *Angew. Chem., Int. Ed.* **2003**, *42*, 768–772.
16. Seemann, R.; Brinkmann, M.; Pföhl, T.; Herminghaus, S. *Rep. Prog. Phys.* **2012**, *75*, 016601.
17. Song, H.; Chen, D. L.; Ismagilov, R. F. *Angew. Chem., Int. Ed.* **2006**, *45*, 7336–7356.
18. Beletskaya, I. P.; Cheprakov, A. V. *J. Organomet. Chem.* **2004**, *689*, 4055–4082.