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Polymer Networks as Carrier for Organo Catalysts within Continuously Driven Microfluidic Reactor Systems

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FINAL REPORT

1 General Information

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2 Summary

Continuous flow reactions using gel-bound organo-catalysts in a microfluidic reactor is an attractive approach in organic synthesis. Here, we have synthesized various catalytic monomers from various functional organo-catalyst and polymerized using photolithography to form polymeric gel dots with different compositions of catalyst, gelling agent and crosslinker. The morphology of the gel dots was evaluated by optical and Laser 3D microscopy. Swelling properties of the gel dots were determined in different reaction solvent mixtures and at different temperatures. The synthesized gel-bounded organocatalysts were inserted into a microfluidic reactor (MFR) and used for conducting different organic reactions like Knoevenagel reaction, Aldol reaction, and Baylis-Hillman reaction under mild conditions. The conversion of the reaction was determined mainly by nuclear magnetic resonance (NMR) as an offline method after collecting elute from the MFR for respective times (less the residence time). Reaction parameters like solvent, flowrate, concentration of reactants, and temperature were optimized. In total reactions could be performed with less catalyst and with similar selectivity as respective batch reactions.

Zusammenfassung

Die kontinuierliche Flussreaktionen mit gelgebundener Organokatalysatoren in einem mikrofluidischen Reaktor ist ein attraktiver Ansatz für die organische Synthese. Hier haben wir verschiedene katalytische Monomere aus verschiedenen funktionellen Organokatalysatoren synthetisiert und mit Hilfe der Photolithographie polymerisiert, um polymere Gelpunkte mit unterschiedlichen Zusammensetzungen von Katalysator, Gel-bildendes Monomer und Vernetzer zu bilden. Die Morphologie der Gelpunkte wurde durch optische und Laser-3D-Mikroskopie bewertet. Die Quelleigenschaften der Gelpunkte wurden im verschiedenen Reaktionslösungsmittelmischungen und verschiedenen Temperaturen bestimmt. Die synthetisierten gel-gebundenen Organokatalysatoren wurden in einen mikrofluidischen Reaktor (MFR) eingesetzt und für die Durchführung verschiedener organischer Reaktionen wie Knoevenagel-Reaktion, Aldol-Reaktion und Baylis-Hillman-Reaktion unter milden Bedingungen verwendet. Der Umsatz der Reaktion wurde hauptsächlich durch kernmagnetische Resonanz (NMR) als Offline-Methode bestimmt, nachdem das Eluat aus dem MFR für entsprechende Zeiten (abzüglich der Verweilzeit) gesammelt wurde. Die Reaktionsparameter wie Lösungsmittel, Durchflussrate, Konzentration der Reaktanten und Temperatur wurden optimiert. Insgesamt konnten die Reaktionen mit weniger Katalysator und mit ähnlicher Selektivität wie die entsprechenden Batch-Reaktionen durchgeführt werden.

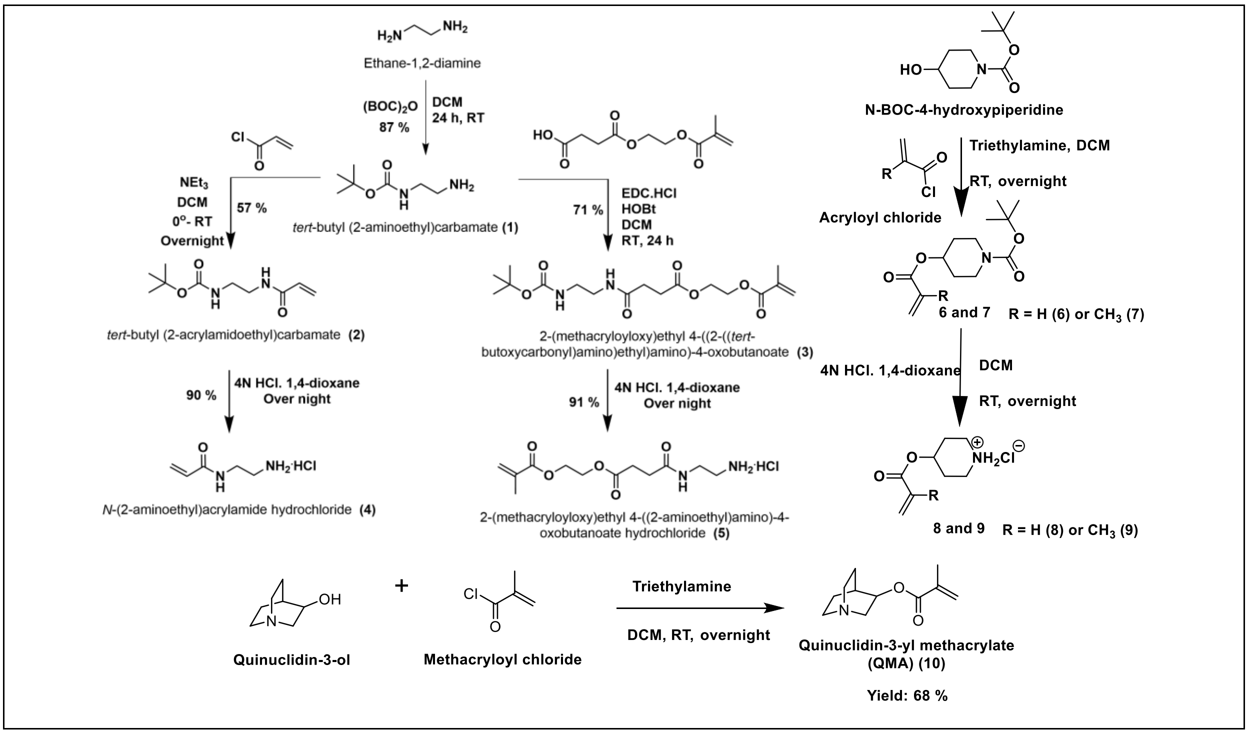
3 Progress Report

Continuous flow reactions using gel-bound organo-catalysts in a microfluidic reactor is an attractive approach in organic synthesis due to interesting advantages such as the permanent production of catalyst-free products, easy product isolation by evaporation, high mass and heat transfer, online detection of reactions and an adjustment of reaction parameters while the reaction is already running[1,2]. Further, organo-catalysts covalently immobilized in the hydrogel provides more accessibility of catalysts inside a microfluidic reactor chamber as compared to the accessible number of surface-bound catalysts, due to the diffusion of reactants within the swollen hydrogel dots. Flow reactor can be scaled down to smaller size and are known as microfluidic reactors (MFR). They can be coupled with different monitoring techniques, such as nuclear magnetic resonance spectroscopy (NMR), high performance liquid chromatography (HPLC), infra-red (IR), ultraviolet/visible (UV/Vis) spectroscopy as well as mass spectrometry[3-6]. Furthermore, microfluidic reactors are considered safer as reaction can be performed using small quantity of reactants and thus allows the use of highly reactive or even toxic reagents fairly easily. Catalytic functionalities are integrated within the cross-linked polymeric networks supporting its reusability and long-term activity. Further, the swelling in presence of solvents leads to enhanced accessibility of the catalytic sites present in the bulk of the polymer, contrary to the solid catalyst which only allows the access to sites available on its surface. Similarly, various polymeric networks have been developed in the form of micro- or macrogels with the loading of various catalysts to perform several organic reactions, such as the aldol reaction, dimerization, Knoevenagel reaction, Baylis–Hillman reaction, Mannich reaction, etc., in the batch method[7]. Furthermore, packed-bed flow reactors are a type of reactor that uses a dense assembly of a catalytically active polymeric material as a carrier to facilitate chemical reactions. They require high pressure, the high loading of catalysts and a fixed, non-active volume in the flow reactor[8]. However, loosely crosslinked polymer networks are mechanically rather weak; hence, the polymer network structure collapses at high pressure during the flow reaction. To overcome the above limitations, formation of micro-structures of polymeric gel dots via photolithography facilitate the stabilization of polymeric networks leading to high conversion rate during the microfluidic reactions.

Catalysts as well as enzymes embedded in polymer gels with high cross-linker content for microfluidic reactions have already been shown[9]. Further, our research group demonstrated organocatalytic reactions, like asymmetric aldol reaction, reductive dimerization, Knoevenagel reaction using polymer networks containing organo-catalysts in continuously operated microfluidic reactors[10-12]. To extend the scope of the organocatalysis using microfluidic reactor, we proposed the synthesis of various catalytic monomers based on organo-catalysts and polymerization via photolithography in various composition of catalyst, gelling agent and cross-linker in the form of gel dots with different geometry and studying their physicochemical properties using various techniques. The developed polymeric gel dots were used as catalysts to perform various organocatalysis reactions, like aldol reaction, Knoevenagel reaction, and Baylis-Hillman reaction. Optimization of the microfluidic reactions in terms of reaction solvent and temperature were done. Further, the versatility of the reactions was determined by screening of various reactants.

Synthesis of catalytic monomers:

Various catalytic monomers were synthesized by nucleophilic substitution of monofunctional organo-catalysts at the acyl group of methacrylic/acryloyl chloride in presence of triethylamine as a base (Scheme 1) for overnight at room temperature. After completion of the reaction, the reaction mixture washed with water, saturated sodium carbonate, and brine to remove salts and unreacted acid then further purification by vacuum distillation or chromatography. The synthesized catalytic monomers were directly used for preparation of polymeric gel dots[13,14].



Scheme 1. *Reaction scheme showing the synthesis of some selected catalytic monomers*

Preparation of polymeric gel dots:

The obtained catalytic monomers were used for the preparation of polymeric gel dots. For the construction of the MFR, the synthesized catalytic monomers were immobilized in the reactor as gel dots via photopolymerization using methyl methacrylate (MMA) or *N,N*-dimethylacrylamide (DMAM) as the gelling agent and *N,N*-methylenebis(acrylamide) (MBAM) or ethylene glycol dimethacrylate (EGDMA) as a crosslinker to obtain various compositions of gel dots. Exemplary conditions are given in Table 1.

Table 1: Fabrication of various polymer gel dots with polymerization parameters

Composition code	Catalytic monomer	Gelling Agent/ Complimentary monomer	Crosslinker	UV irradiation time (s)	UV intensity (W)	Number of gel dots
A	Tertiary amine (DMAPAM), 90 %	DMAM, 9 %	MBAM, 1 %	8	0.42	202
B	Primary amine (5), 90 %	MMA, 9 %	EGDMA, 1 %	14	0.42	202
C	Primary amine (4), 90 %	DMAM, 9 %	MBAM, 1 %	90	1.28	202
D	PA (8), 90 %	DMAM, 5 %	MBAM, 5 %	16	0.42	662
E	PA (8), 50 %	DMAM, 45 %	MBAM, 5 %	11	0.42	662
F	PMA (9), 90 %	MMA, 5 %	EGDMA, 5 %	10	0.42	662
G	PMA (9), 50 %	MMA, 45 %	EGDMA, 5 %	35	0.84	662
H	QMA (10), 90 %	MMA, 5 %	EGDMA, 5 %	90	1.28	662

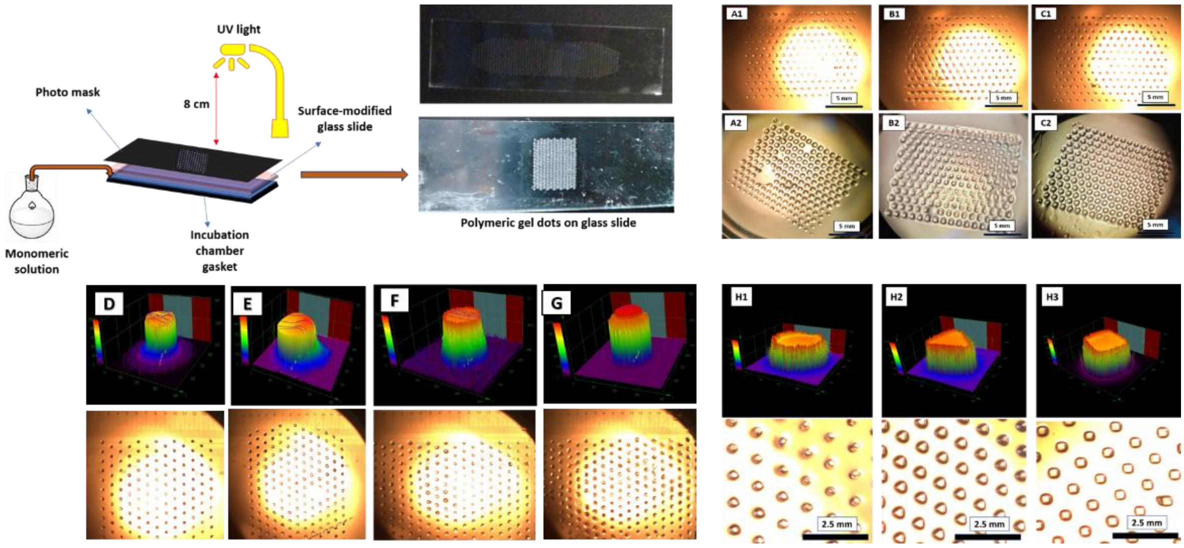


Figure 1. Graphical representation of preparation of polymeric gel dots and optical microscopy images of gel dots with different compositions, A, B, C, D, E, F and G. Series 1 representing the dried gel dots and series 2 after swelling in the solvent mixture, DMSO: 2-propanol: water (*v:v:v* = 2:2:1), for 12 h and H1) spherical H2) triangle and H3) cylindrical. The top images were captured by a confocal 3D laser microscope and the bottom images were captured by light microscopy.

To facilitate the fabrication of polymer gel dots on the surface of conventional microscopic glass substrate, surface modification was performed with methacrylate siloxanes to participate in the polymer network of polymer gel dots. This treatment provided a better adhesion of the polymer gel dot framework to the glass substrate and ensured that the polymer gel dots are not leached off during purification of polymeric networks and performing flow reactions.

Polymer gel dots were fabricated by performing UV assisted photopolymerization of monomeric contents. Different polymer gel dots were prepared by varying relative ratios of monomers (total concentration of monomers: 15 mmol %) and different duration of UV irradiation as presented in Table 1. Similarly, the gel composition **H** was used for fabrication of different geometries (cylindrical, triangle and square) of gel geometries using respective photomask as shown in Figure 1. The influence of polymeric gel geometries was studied in the microfluidic reactor system and the catalytic activity was determined.

The swelling of the gels provided a significant change in organo-catalysis, because, during the swelling process, the polymeric networks stretch to form a large mess-like structures. As a result, the accessibility of the catalytic sites increases for catalysis. Similarly, the catalytic activity of the gel dots increases with an increase in uptake of the reaction solvent. To evaluate the swelling properties of the gels, bulk gels with different compositions were prepared with the parameters shown in Table 1. The degree of swelling with respect to weight and volume was determined. The gel composition **A, B** and **C** data are presented in the published article only[14], while the gel compositions **D, E, F** and **G** showed best swelling of 133 to 200 % of change in volume in the solvent mixture DMSO : Methanol (7:3) at room temperature. The supported gel dots were stable even at 40 °C. Similarly, the gel composition, **H** showed a degree of swelling of around 600 % with respect to volume. These results indicate that the solvent system was suitable for the further investigation of catalysis.

Organocatalysis in microfluidic reactor system

Different organic reactions have been investigated during the funding period: Knoevenagel reaction[14], aldol reaction[12], reductive dimerization of nitrosobenzenes[11], and Baylis-Hilman reaction[13]. In the following, only recent not published results are highlighted.

Knoevenagel reaction:

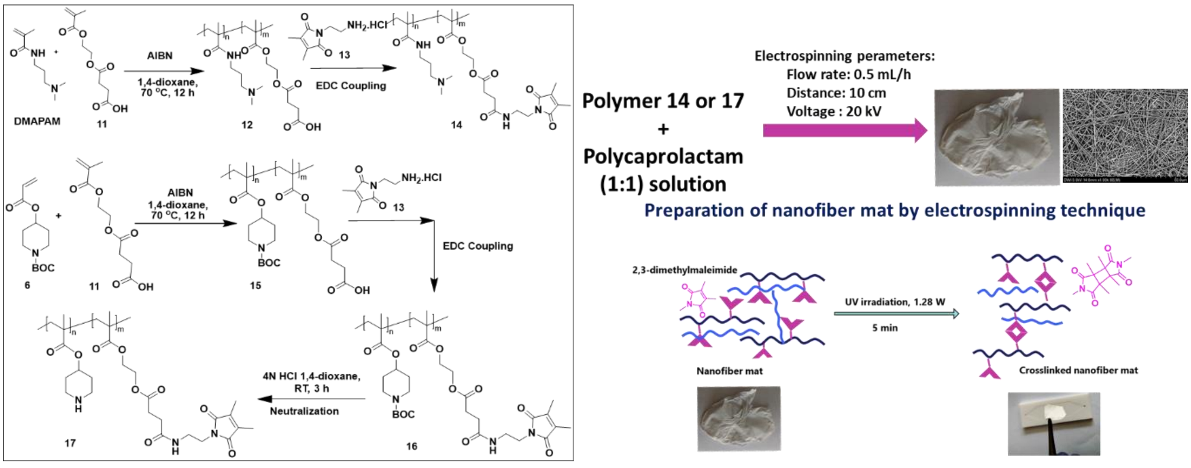
The general reactor setup was completed according to a previous report[12]. For the catalysis of the Knoevenagel reaction to synthesize pharmacologically interesting curcumin derivatives in MFR, piperidine based hexagonal shaped polymer networks (**D** to **G** gel dot compositions as shown in Table 1) containing 662 dots were used[15]. The number of dots was increased for this reaction to obtain longer residence times. The flow rate of the MFR reaction changes from 2 μL/min for pre-swelling to 0.5 μL/min for the reaction yielding a residence time of 3.5 h. Moreover, the reactants passed through the MFR using single syringe as reactant reservoir. From all the reactions, the composition of **G** showed significantly higher conversion due to higher swelling in the reaction solvent (DMSO: methanol, 7:3). Accordingly, we have performed the synthesis of curcumin derivatives by reaction between various aldehydes and curcumin (2:1

mole ratio) using gel dots with composition **G** in MFR and the conversion of the reaction determined by off-line ^{1}H NMR as given in Table 2.

Table 2: Conversion of the reaction between different aldehydes and curcumin in MFR.

Entry	Reactants (2:1 mmol ratio)	Gel dot composition	T [°C]	t [h]	Conv. [%]
1	4-nitrobenzaldehyde + Curcumin	G	40	72	72
2	Benzaldehyde + Curcumin	G	40	72	47
3	4-fluorobenzaldehyde + Curcumin	G	40	72	13
4	4-chlorobenzaldehyde + Curcumin	G	40	72	3
5	4-bromobenzaldehyde + Curcumin	G	40	72	22
6	3-chlorobenzaldehyde + Curcumin	G	40	72	31
7	4-methoxybenzaldehyde + Curcumin	G	40	72	16

To extend the scope of the continuous microfluidic reactions, Knoevenagel reactions were performed using nanofiber mats of catalytic polymers instead of polymeric gel dots. This research work was done in collaboration of Prof. Dr. Andreas Herrmann and Dr. Barbara Dittrich, DWI – Leibniz-Institut für Interactive Materialien[16]. Synthesis of catalytic polymer **14** and **17**, fabrication and photo crosslinking of the nanofiber mat were represented in Figure 2.



Synthesis of catalytic polymers from the catalytic monomers

Photo crosslinking of the nanofiber mat

Figure 2. Schematic representation of synthesis of catalytic polymers **14** and **17**, fabrication and photo crosslinking of the nanofiber mat.

The crosslinked composite nanofiber mats with poly(caprolactam) and polymer **14** (PCLPTAPC11) and polymer **17** (PCLPPAPC11), respectively, were cut into a square shaped piece (2.3 cm X 2.3 cm and approximately 8 mg) and were used as catalyst in the MFR instead of polymeric gel dots to perform Knoevenagel reactions between different aldehydes and malononitrile. The reaction setup and conditions as same as the reaction with the gel dot composition **A** to **B**. The conversion of the reaction was determined by off-line ^{1}H NMR as given in Table 3. The results showed that the conversion of the reaction was increased to almost 100 % with the high reactive aldehydes, 4-nitrobenzaldehyde, 3-chlorobenzaldehyde and the conversion was slightly lower for less reactive aldehyde, 4-methoxybenzaldehyde approximately 75 %. These nanofiber mats are promising substitutes for the gel dots, since they have larger surface areas and smaller gel dimensions facilitating the diffusion of reactants and products in and out of the gels.

Table 3: Conversion of the reaction between different aldehydes and malononitrile in MFR containing nanofiber mats.

Entry	Reactants (1:2 mmol ratio)	Composition	t [h]	Conv. [%]
1	4-nitrobenzaldehyde + malononitrile	PCLPTAPC11	8	100
2	4-nitrobenzaldehyde + malononitrile	PCLPPAPC11	8	100
3	3-chlorobenzaldehyde + malononitrile	PCLPTAPC11	8	100
4	3-chlorobenzaldehyde + malononitrile	PCLPPAPC11	8	96
5	4-methoxybenzaldehyde + malononitrile	PCLPTAPC11	8	74
6	4-methoxybenzaldehyde + malononitrile	PCLPPAPC11	8	76

Baylis-Hillman Reaction:

Baylis-Hillman reaction with different aldehydes and acrylonitrile were performed in continuous microfluidic reactor system using the hexagonal shaped polymer networks containing polymer dots composition **H** (662 pieces) as in Table 1. After successful assembly of the microfluidic reactor, organocatalysis reaction was carried out at 50 ºC. The conversion of the reaction was determined using off-line ^{1}H NMR method with 8 h collection of eluent sample excluding the residence time (3.5 h). The conversion was very good with the more reactive aldehydes like 2-nitrobenaldehyde, 3-nitrobenaldehyde, 4-nitrobenaldehyde, 4-cyanobenzaldehyde and 4-bromobenaldehyde with 90-100 % while, the conversion was lower for less reactive aldehydes like benzaldehyde and 4-methoxybenzaldehyde, as given in Table 4[17].

Table 4: Determination of reaction conversion with the Baylis-Hilman reaction between different aldehydes and acrylonitrile. The conversion was determined by off-line ^{1}H NMR method.

Entry	Reactants (1:2 mmol ratio)	Gel dot composition	T [°C]	t [h]	Conv. [%]
1	2-nitrobenzaldehyde + acrylonitrile	H	50	8	96
2	3-nitrobenzaldehyde + acrylonitrile	H	50	8	98
3	4-nitrobenzaldehyde + acrylonitrile	H	50	8	100
4	4-cyanobenzaldehyde + acrylonitrile	H	50	8	83
5	4-flurobenzaldehyde + acrylonitrile	H	50	8	59
6	4-bromobenzaldehyde + acrylonitrile	H	50	8	91

7	3-chlorobenzaldehyde + acrylonitrile	H	50	8	62
8	benzaldehyde + acrylonitrile	H	50	8	23
9	4-methoxybenzaldehyde + acrylonitrile	H	50	8	16

Further, different geometries (cylindrical, triangle and square) of the polymer gel dots of gel dot composition **H** were used as a catalyst in the microfluidic reactor. The conversion of the reaction and pressure created during the continuous microfluidic reaction between 4-nitrobenzaldehyde and acrylonitrile were given in the Table 5. The conversion of the reaction with geometry of gel dots, cylindrical, square was recorded 100 %, whereas triangle shaped gel dots showed 90 %. Further, the pressure in the reactor also reached 9 -13 mbar during pre-swelling process at flow rate of 2 µL/min and then 3 to 5 mbar while performing the reaction at flow rate of 0.5 µL/min. The results suggested that the geometry of gel structures, cylindrical and square facilitated higher catalytic activity as compared to the triangle shaped gel dots due their surface area, cylindrical, triangle and square gel dots, 480 mm^2, 391 mm^2 and 493 mm^2, respectively. This research work was done in collaboration of Prof. Dr. Andreas Richter, TU Dresden[16].

Table **5**: Continuous microfluidic reaction between 4-nitrobenzaldehyde and acrylonitrile using different geometry of gel dots.

Composition	**Geometry of gel dots**	**Conversion (%)**	**Pressure (mbar)**	
			Pre-swelling of gel dots at flow rate of 2 µL/min	**Reaction process at flow rate of 0.5 µL/min**
C	Cylindrical	100	12±5	5±5
C	Triangle	90	9±5	3±2
C	Square	100	13±5	4±5

Long-time microfluidic reaction between 4-bromobenalidehyde and acrylonitrile was performed to understand the efficiency of continuous process of the reaction for 6 days. The conversion of the reaction was calculated around 70 to 80 % until 5 days and then was slightly decreased (66 %) due to accumulation of the product on the polymer networks. These results suggest that the turnover number of the catalyst in the continuous microfluidic reactions is enhanced as compared to the other conventional method.

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4 Published Project Results

4.1 Publications with scientific quality assurance

11. C. J. Schmiegel, P. Berg, F. Obst, R. Schoch, D. Appelhans, D. Kuckling, „Continuous flow synthesis of azoxybenzenes by reductive dimerization of nitrosobenzenes with gel-bound catalysts" *Eur. J. Org. Chem.* **2021**, 1628-1636. DOI: 10.1002/ejoc.202100006
12. C. J. Schmiegel, R. Baier, D. Kuckling, „Direct asymmetric aldol reaction in continuous flow using gel-bound organocatalysts" *Eur. J. Org. Chem.* **2021**, 2578-2586. DOI: 10.1002/ejoc.202100268
13. A. Kumar, D. Kuckling, L. Nebhani, „Polymeric microparticles containing quinuclidine as a catalyst for the Baylis-Hillman reaction" *ACS Appl. Polym. Mater.* **2022**, *4*, 8996–9005. DOI: 10.1021/acsapm.2c01330.
14. N. Killi, J. Bartenbach, D. Kuckling, "Networks Containing Amine Derivatives as Organo-catalysts for Knoevenagel Reaction within Continuously Driven Microfluidic Reactors" *Gels* **2023**, *9*, 171. DOI: 10.3390/gels9030171
15. N. Killi, K. Rumke, D. Kuckling, "Synthesis of curcumin derivatives via Knoevenagel reaction within continuously driven microfluidic reactor system assisted polymeric networks containing piperidine as a catalyst" *Gels* **2025**, *11*, 278. DOI: 10.3390/gels11040278

Manuscripts in preparation:

16. N. Killi, K. Rumke, B. Dittrich, A. Herrmann, D. Kuckling, “Fabrication of catalytic polymers as nanofiber matrices and organocatalysis of Knoevenagel reaction in continuously operated microfluidic reactor”
17. N. Killi, A. Kumar, L. Nebhani, F. Obst, A. Richter, B. Reineke Matsudo, T. Zentgraf, D. Kuckling, “Integrating organo-catalyst within the framework of polymeric gel for catalyzing Baylis – Hillman reaction in continuous flow reactor system” (ACS Applied Polymeric Materials)

4.2 Other publications and published results

Attended conference (Poster presentations)

1. N. Killi: Organic reactions in continues flow using gel-bounded organo-catalysts, conference on Adaptive Polymers and Systems, RWTH Aachen University, Aachen, September 12-14, 2022
2. N. Killi: Polymer Networks as Carriers for Organo-catalysts within Continuously Driven Microfluidic Reactor Systems, conference on 14th Advanced Polymers via Macromolecular Engineering” (APME23) in Paris, France, April 23-27, 2023
3. N. Killi: Gel-bounded Organo-catalyst for Baylis-Hillman reaction in Continuously Driven Microfluidic Reactor, Summer School on Catalysis: Understanding and applications, IMT-Mines, Albi, France, June 17-22, 2024.

4.3 Patents (applied for and granted)

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