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Polymer/carrier composites as materials and reactors for organic synthesis

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Abstract

In this work new polymer/carrier composites are described which serve as novel materials in flow-through reactors for polymer-supported organic solution-phase synthesis. Monolithic polymer/carrier columns are prepared by a new precipitation polymerization process inside the void pore volume of megaporous glass carrier materials. Chemical functionalization of the internal polymer phase with chlorosulfonic acid or trimethylamine generates small, interconnected ion-exchange resin beads with a diameter of 1–3 μm which can be used for a large variety of organic syntheses. These monolithic rods are incorporated into an appropriate casing and can conveniently be operated in the flow-through mode. Important successful applications are polymer-assisted solution-phase reductions, oxidations and Horner–Emmons olefinations. Additionally, the use of these monolithic columns as catalytic microreactors and their performance in selected reactions are described.
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1. Introduction

Based on the pioneering work by Merrifield [1] in the field of polymer supports the technique of polymer-attached reagents for use in solution-phase organic synthesis has seen a renewed interest in the last few years [2–5]. It has been proven that this technique is a powerful alternative to classical organic synthesis in solution. Here reagents or catalysts are immobilized on a polymeric phase or inorganic support which promote transformation of substrates in solution. The major advantages of this

hybrid solid-phase/solution-phase process lie in the simple purification of the products, which remain in the liquid phase, and the possibility to use the polymer-bound reagent in excess to drive reactions to completion.

State of the art in polymer-supported synthesis is to use gel-like or macroporous resin beads. Most often crosslinked polystyrenes or different types of ion-exchange resins are utilized for this purpose. The particle diameters are typically in the range of up to 500 μm, on which the reagents or catalysts are immobilized [2–5]. Activation of the resin and reaction are generally carried out manually in a time consuming way of several single steps in stirred vessels in a batch mode. Due to the large dimensions of the employed polymer particles and the unfavourable flow conditions in commercial vessels lower

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rates of reaction compared to classical solution phase synthesis have been observed [6–8]. Therefore, the possibility to combine this hybrid solid-phase/solution-phase technique with a flow-through process employing polymer particles of pronounced smaller size at the same time would create an ideal almost workup-free process for automated organic synthesis [9].

However, three key criteria for the construction of monolithic flow-through microreactors have to be met. These are good accessibility of the immobilized reagent, a high loading of the polymeric phase and a mechanically stable polymer phase. All three criteria can be controlled by the degree of crosslinking of the polymer support [10]. To obtain a stable monolithic polymer phase, which only swells or shrinks imperceptibly in organic solvents, a high degree of crosslinking (30–40% of crosslinker) is necessary, which is unfavourable for the accessibility and loading of the immobilized reagents. Despite this high degree of crosslinking, embedding the polymeric monolith in a tube to create a flow-through reactor still results in wall effects [11]. For kinetic reasons and accessibility of the reagents a low degree of crosslinking is desired. This leads to gel-like particles which as a result of good swelling in organic solvents ensure a good accessibility of the immobilized species. However, embedded in tubes these particles either block the flow when swollen or, when shrunk, create a gap between the inner wall of the reactor and the polymer which results in bypassing of the solution.

In this work a new polymer/carrier composite as the key component for a monolithic flow-through microreactor for polymer-supported organic synthesis is presented. Due to a precipitation polymerization process small gel-like polymer particles (1–3 μm diameter) can be introduced in the pore volume of a monolithic megaporous carrier material [12], preferably in the shape of a cylindrical rod. The term ''carrier'' means a solid support for the immobilization of the polymer particles. It is not used in the sense as in chromatography, where a carrier is the flowing medium or solvent. The small size and the low degree of crosslinking, which can be varied from 2 to 20%, ensure a high loading of the polymer and good accessibility of the supported reagents. Additionally, having a polymer phase inside a fixed

matrix of carrier material leads to a reactor interior with a stable shape. The outer dimensions of the rod stay stable while the polymer particles can only swell and shrink in the open pore volume of the carrier material. Problems like bypassing or blocking are avoided.

2. Preparation of monolithic composite microreactors

At the Institut für Chemische Verfahrenstechnik a process for the precipitation polymerization of cross-linked poly(styrene–co-divinylbenzene) and poly-(vinylchlorobenzene–co-divinylbenzene) inside the void pore space of a megaporous carrier material (support) has been established [12]. Due to the requirements (high porosity, large pore diameters and chemical resistance) for the carrier material, porous glass carriers with a porosity $\varepsilon \approx 0.4$ and pore sizes of 50–300 μm are the best choice [12]. The result of the polymerization process is an agglomeration of gel-like polymer particles with a diameter of 1–3 μm inside the void pore space of the carrier material. The particles are interconnected by polymer bridges, so that they cannot be washed out of the carrier material even under forced convective flow and remain stable in the pore space [12].

The new polymerization process can be employed for almost every shape of monolithic carrier material. To create a flow-through microreactor cylindrical glass rods with a diameter of 5.3 mm and a length of 110 mm are used. The combination of the megaporous carrier material with its internal polymer phase together with convective flow through the microreactor ensures enhanced mass transfer and shorter diffusion paths of molecules in the pore space [13].

Following the polymerization process a chemical functionalization of the polymer phase is carried out. The poly(styrene–co-divinylbenzene) matrix is sulfonated with chlorosulfonic acid whereas poly-(vinylchlorobenzene–co-divinylbenzene) is aminated with trimethylamine to obtain acidic and basic ion-exchange resins, respectively, with a loading capacity of about 1 mmol per column. In the first case the result is a polymer containing sulfonic acid sites, whereas in the second case strong basic quarternary
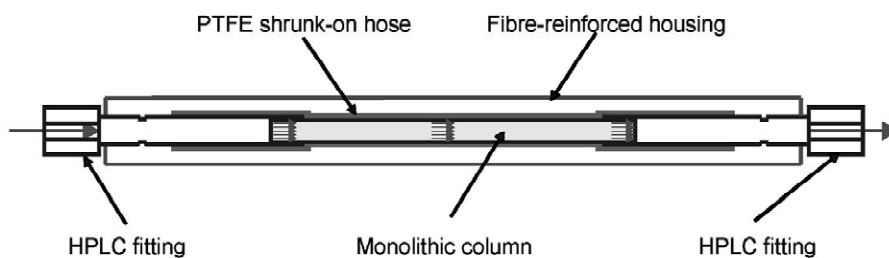
Fig. 1. Cross-sectional drawing of the composite microreactor (PTFE=polytetrafluoroethylene).

ammonium chloride sites are formed. The generated ion-exchange resin particles can be loaded with desired ionic reagents or catalysts to perform solid-supported organic solution phase synthesis.

The monolithic glass rod with its internal functionalized polymer phase as the key component for the flow-through microreactor is put in between two constructed connecting pipes with an outer diameter of 6.35 mm. This system is sealed with a solvent-resistant PTFE shrunk-on hose to avoid wall effects. This is followed by encapsulation with a pressure-resistant fibre-reinforced epoxy-resin material as a casing for the microreactor. In order to be able to connect the microreactor to a conventional high-performance liquid chromatography (HPLC) pump and make it efficient for laboratory use two standard column end fittings are added to the connecting pipes (Fig. 1).

3. Applications of the monolithic microreactor

The developed composite microreactors have been successfully applied in several different fields of polymer supported organic chemistry such the immobilization of ionic reagents and catalysts. Fig. 2 gives an overview on the possible applications of the microreactors. It is operated in a closed circulation loop to drive reactions to completion.

3.1. Ionic bonded reagents

Recyclability of stoichiometrically employed reagents is a major issue in polymer-assisted solution phase synthesis. Anionic exchange resins fulfil this requirement in the most convenient way as they can be easily reloaded with various desired anions. Therefore the composite microreactor with the ami-
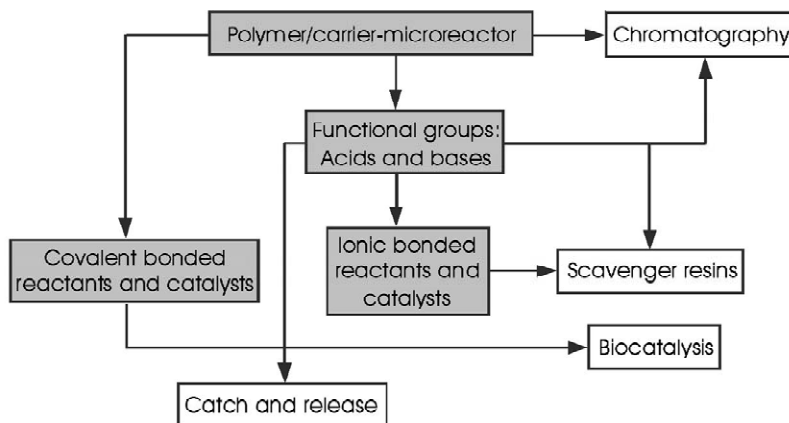

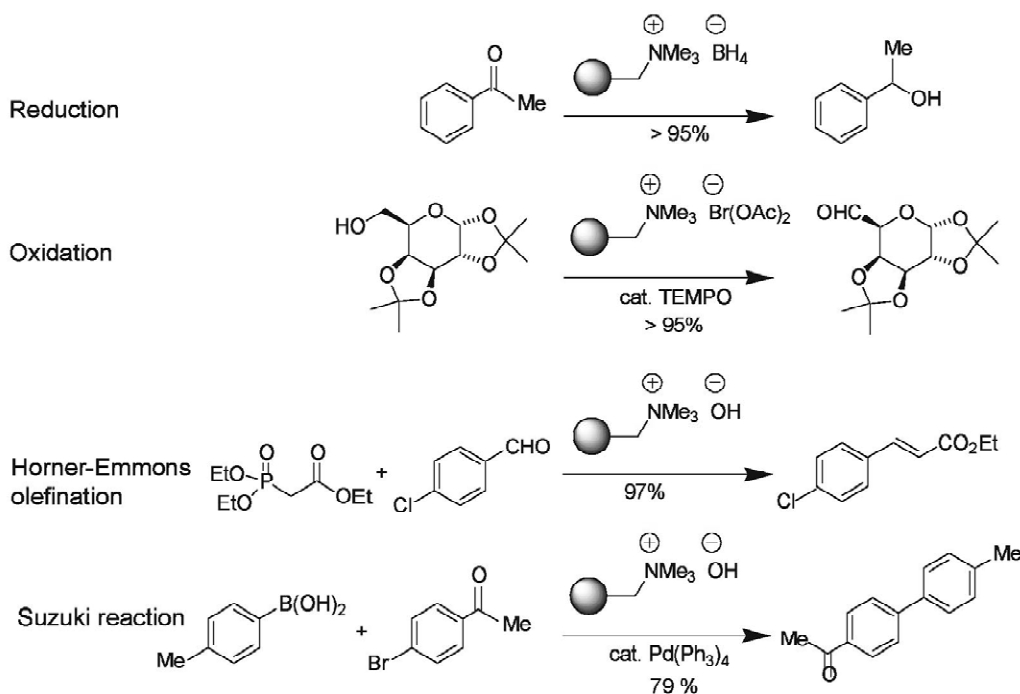Fig. 2. Possible applications of the new monolithic microreactors.

Fig. 3. Examples of successfully performed organic syntheses with ionic bonded reagents in composite microreactors.

nated polymer phase is the ideal tool to perform organic syntheses with various ionic bonded reagents. As depicted in Fig. 3 borohydride as a reducing ion was attached to the functionalized polymer to promote reductions of aldehydes and ketones [13] to almost complete conversion. The same results are obtained using bound bromate(I) anions to perform oxidation reactions in the presence of the catalyst TEMPO (TEMPO=2,2,6,6-tetra-methylpiperidin-1-oxyl, a stable free radical) [14]. Immobilized hydroxide ion is the fundamental species for performing more challenging organic transformations such as Horner–Emmons olefinations (see Refs. [15,16]) and Suzuki cross-coupling reactions which can be conducted with the composite microreactor highly efficiently in terms of yield, purity and reaction time [17].

3.2. Noble metals as catalysts for hydrogenations

The use of ion-exchange resins is a very elegant way for precipitation of well dispersed noble metals in or on a polymeric particle [18]. Isolated ion-exchange groups ensure a very homogeneous distribution of metal salts throughout the polymeric phase. Treatment of the polymer/carrier microreactor with desired noble metal salts, followed by a reduction process with borohydride or hydrazine, generates small and well dispersed metal particles in the polymer which act as catalysts for chemical reactions. Table 1 gives a summary of examples of this technique employed to the composite microreactors.

The obtained catalytic microreactors have proven their efficiency for hydrogenations of aromatic nitro

Table 1
Examples of noble metal loaded ion-exchange resins as catalysts

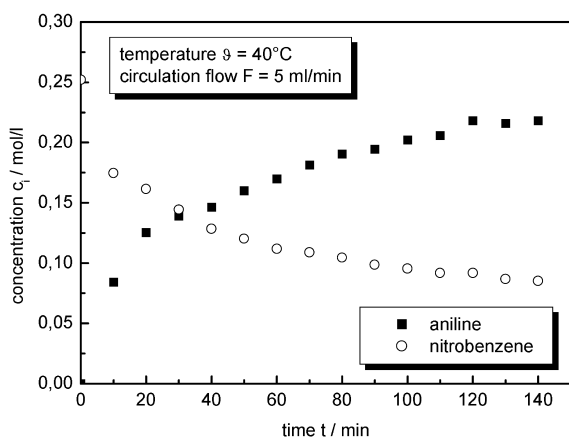| Type of polymeric phase	Loading with	Reducing agent	Obtained catalyst
Basic, aminated	Na_2PdCl_4	$NaBH_4$ or NH_2NH_2	Pd
Basic, aminated	Na_2PtCl_4	$NaBH_4$ or NH_2NH_2	Pt
Acidic, sulfonated	$Ni(OCOCH_3)_2$	$NaBH_4$	Ni

Fig. 4. Conversion of nitrobenzene to aniline in a composite microreactor loaded with Pd catalyst (parameters are given in the legend).

compounds using hydrazine as a reducing agent to perform chemical reactions under very mild conditions. Experiments using the most simple aromatic nitro compound, nitrobenzene, as reactant have shown that the hydrogenation to aniline in the presence of Pd(0) catalyst proceeds very quickly compared to other organic syntheses and leads to high yields of the desired product (Fig. 4).

3.3. Covalent bonded catalysts

Salen complexes have seen widespread application

in enantioselective catalysis [19]. Depending on the metals employed a large range of reactions can be conducted including kinetic resolutions [20] of oxiranes and cycloaddition reactions. Here, we attached a heterodimeric Salen ligand via a glutaric acid linker to the glass/polymer composite material and conducted a kinetic resolution of *rac*-epibromohydrine in tetrahydrofuran (THF) in the presence of 1.5 equivalents of water. The reaction proceeded in excellent yield with excellent enantioselectivity at room temperature to almost exclusively yield the (*R*)-configured ring-opening product (Fig. 5). The enantiopurity of the product was achieved after derivatization to the isopropylidene protected diol using a cyclodextrin-based gas chromatography (GC) column. It is known that epibromohydrine rapidly undergoes interconversion between the two enantiomeric forms, so that this is a good example of a dynamic kinetic resolution promoted by an immobilized chiral metal complex [21].

4. Experimental

4.1. Preparation of polymer/glass monoliths and application in organic synthesis

Polymerization: Vinylbenzylchloride (45 g) and divinylbenzene (3.9 g; 65% ethylbenzene) were dissolved in C_{14}–C_{17} *n*-alkanes (300 ml). After dissolu-
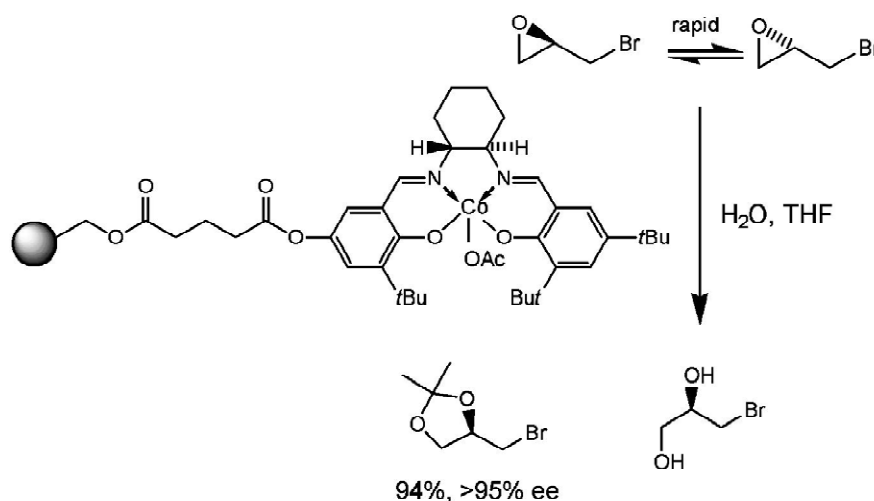

Fig. 5. Enantioselective conversion of epibromohydrine with a Salen activated microreactor.

tion of azoisobutyronitrile (300 mg) porous glass rods with a diameter of 5.3 mm and a length of 110 mm were immersed in this solution. Air was removed from inside the pore volume by applying a vacuum for a short time. After heating at 70 °C overnight, the rods were cleaned of any adhering polymer and rinsed with trichloromethane.

Amination: The rods loaded with the polymer were covered with dry toluene and a continuous flow of trimethylamine was passed through this solution. After 4 days the rods were removed from the solution and dried in vacuum. The rods, now functionalized with quarternary ammonium cations, were fitted with a casing and could be used as microreactors.

4.2. Preparation and application of ionic bonded reagents

The microreactors (ca. 0.4 mequiv. capacity), initially loaded with chloride anions, were used for all syntheses described below. All products were characterized by ^{1}H nuclear magnetic resonance (NMR), IR, mass spectrometry (MS), and by correlation with the reported data.

4.3. Borohydride reduction

The microreactor was flushed with 10% aq. sodium borohydride solution (10 ml), followed by water (30 ml) and methanol (15 ml). Then, a solution of acetophenone (60 mg, 0.5 mmol) in 5 ml methanol was pumped through the reactor (2.0 ml/min) at 60 °C for 6 h. The reactor system was rinsed with methanol (15 ml). The combined reaction mixtures were concentrated in vacuo to yield pure 1-phenylethanol (61 mg, 100%).

4.4. TEMPO-catalyzed oxidation

The microreactor was washed successively with 1 M NaOH (20 ml), water (20 ml), 2 M HBr (20 ml), water (20 ml), methanol (20 ml), and anhydrous dichloromethane (30 ml). Then, a solution of diacetoxyiodosobenzene (1.5 ml in 10 ml anhydrous dichloromethane) was circulated overnight under nitrogen atmosphere, and the reactor was washed with anhydrous dichloromethane (20 ml). A solution

of alcohol (0.125 mmol) and TEMPO (0.005 mmol) in anhydrous dichloromethane (10 ml) was allowed to circulate through the microreactor under a nitrogen atmosphere for 6 h. The reactor system was washed with dichloromethane (15 ml), and the combined organic solutions were concentrated in vacuo to yield analytically pure product (yield >99%).

4.5. Horner–Emmons olefination

The microreactor was loaded with hydroxide ions (60 ml of 1 M NaOH) followed by successive washing with water (150 ml), methanol (30 ml), and diethyl ether (30 ml). Finally, the reactor was dried in vacuo at room temperature over P_2O_5 for 3 h and then flushed with anhydrous THF (15 ml). After this procedure, a solution of 4-chlorobenzaldehyde (27.3 mg, 0.194 mmol) and triethyl phosphonoacetate (41.4 mg, 0.185 mmol) in anhydrous THF (3 ml) was pumped through the reactor (2.5 ml/min) at room temperature in a cyclic mode. After 2 h the reactor system was rinsed with anhydrous THF (15 ml). The combined organic solutions were concentrated in vacuo to yield target ethyl *p*-chlorocinnamate (only *E*-isomer; 38 mg, 97%).

4.6. Suzuki cross-coupling reaction

The microreactor was washed successively with 1 M NaOH (60 ml), water (150 ml), methanol (15 ml), and anhydrous THF (15 ml). Then, a degassed solution of 4-methylbenzeneboronic acid (25 mg, 0.184 mmol), 4-bromoacetohenone (24 mg, 0.121 mmol), and tetrakis(triphenylphosphine)palladium (7 mg, 0.006 mmol) in anhydrous THF (3 ml) was allowed to circulate through the reactor (2.5 ml/min) at 60 °C under a nitrogen atmosphere for 4 h. The reactor system was rinsed with anhydrous THF (10 ml) and methanol (10 ml). The combined organic mixtures were concentrated in vacuo to yield a white solid. Flash chromatography on silica (cyclohexane–EtOAc, 95:5) afforded pure 4-acetyl-4′-methyl-1,1′-biphenyl (20 mg, 79%).

4.7. Preparation and application of noble metal catalysts

1 mmol of the listed noble metal salts was dis-

solved in 30 ml distilled water and pumped through the reactor with a flow of 1 ml/min. This was repeated once. Then the reactors were washed with distilled water until no metal salts were observed in the effluent. A solution of 50 ml containing 10 mmol of sodium borohydride or hydrazine was produced which was pumped through the reactor with a flow of 1 ml/min. Afterwards the reactor was treated with 50 ml distilled water, 50 ml 1 M hydrochloric acid and 50 ml distilled water with a flow of 1 ml/min each.

The hydrogenation reactions of nitrobenzene were carried out in a recycle mode using 20 ml of methanol as solvent. The concentrations of nitrobenzene were varied from 0.05 to 0.5 mol/l and a circulation flow of 5 ml/min was used.

4.8. Preparation and application polymer-bound Salen complex

A 50-mg amount of poly(vinylchlorobenzene-co-divinylbenzene) resin was added to the solution of Salen glutarate mono-ester (93 mg, 0.15 mmol), cesium iodide (39 mg, 0.15 mmol), and diisopropyl-ethylamine (19.4 mg, 0.15 mmol) in anhydrous dimethylformamide (DMF) (2 ml). The reaction mixture was stirred at 60 °C under nitrogen atmosphere for 24 h and filtered. The collected solid was washed with water, methanol, dichloromethane, and dried in vacuum to give a light-yellow powder (64 mg).

A 56-mg amount of this resin was stirred with the solution of cobaltous acetate tetrahydrate (10 mg, 0.040 mmol) in methanol–toluene (1:1) (1 ml) under a nitrogen atmosphere for 2 h. Then, the resin was filtered, washed with methanol, dichloromethane, toluene–AcOH (9:1), dichloromethane, methanol, dichloromethane, and dried in vacuum to give a brown–greenish resin (Co-Salen resin).

4.9. Dynamic kinetic resolution of rac-epibromohydrin with polymer-bound Salen catalyst

This method, which is well described in [21] allows to convert a racemate completely into one stereo selective product by chemical reaction of only one of the enantiomers and simultaneous isomerization of the remaining enantiomer into the reactive enantiomer. Co-Salen resin (43 mg), epibromohydrin

(137 mg, 1 mmol), water (27 mg, 1.5 mmol), and THF (0.3 ml) were stirred at room temperature for 48 h. The reaction mixture was filtered, and the resin was rinsed with THF (2 ml) and dichlorometane (10 ml). The combined filtrates were concentrated in vacuo to give (*R*)-3-bromo-1,2-propanediol (145 mg, 94%). The corresponding acetonide was prepared using 1% (w/v) camphorsulfonic acid in dimethoxy-propane (chiral GC: capillary column β-hydrodex-PM, 50 m×0.25 mm, Macherey-Nagel, 100 °C, iso-thermal, t_R=40.2, 40.8 min; 95% enantiomeric excess).

5. Conclusion

A new composite microreactor has been developed which combines the advantages of continuous flow-through processes with the diversity of polymer-supported chemical transformations by means of conventional ion-exchange resins. The key component is a novel monolithic composite material consisting of a stable megaporous glass carrier material and an internal functionalized polymer. The megaporous carrier material ensures good convective flow and a low pressure drop and diminishes wall effects due its mechanical stability and the use of appropriate sealing. The new polymerization process generates small interconnected polymer particles which can swell and shrink in the void pore space of the carrier material. The result is a good accessibility of the immobilized reagents. The ability to attach every desired ion to the polymeric backbone by simple ion exchange opens a wide field of applications for polymer-assisted organic synthesis and catalysis in a convenient flow-through mode. The possibility to incorporate the reactor system into any conventional HPLC system makes this concept a cost-effective laboratory tool for organic chemistry which can be automated easily for parallel or multi-step syntheses. In Fig. 6 this is depicted by a flow-sheet. In the left part of the flow-sheet the microreactor and the peripheral equipment can be seen, which is named ''Synthesis Station''. In the right part of the figure the analytical section is given, which allows easy monitoring of the reaction progress by HPLC analysis. All components used are standard HPLC parts.
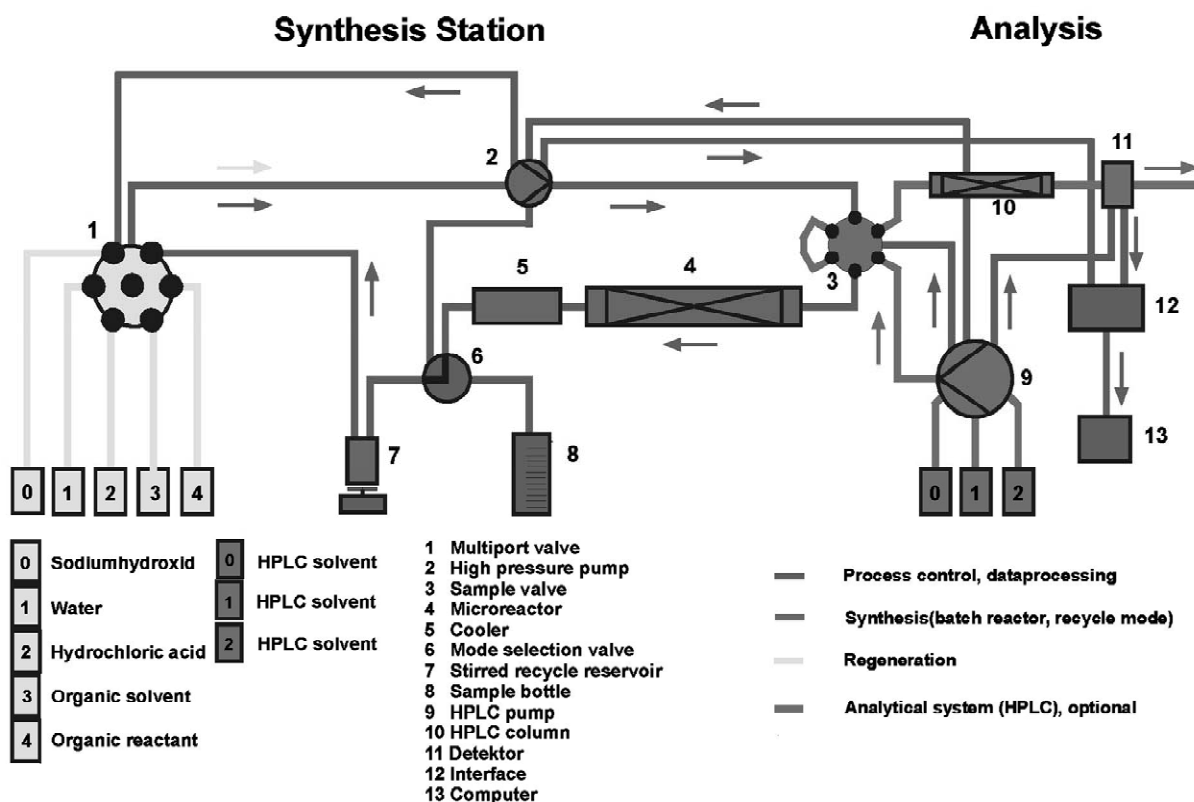
Synthesis Station   ## Analysis

0 Sodiumhydroxid	**0** HPLC solvent
1 Water	**1** HPLC solvent
2 Hydrochloric acid	**2** HPLC solvent
3 Organic solvent	
4 Organic reactant	

1 Multiport valve
2 High pressure pump
3 Sample valve
4 Microreactor
5 Cooler
6 Mode selection valve
7 Stirred recycle reservoir
8 Sample bottle
9 HPLC pump
10 HPLC column
11 Detektor
12 Interface
13 Computer

━━ Process control, dataprocessing
━━ Synthesis(batch reactor, recycle mode)
━━ Regeneration
━━ Analytical system (HPLC), optional

Fig. 6. Example of how to use HPLC equipment for operation of the microreactor.

Acknowledgements

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