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A high parallel reaction system for efficient catalyst research

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ABSTRACT

High throughput screening of homogeneous catalysts in gas reactions (e.g. hydrogen or carbon monoxide) becomes possible in a fully automated way with our new laboratory system. Heart of the system is the high pressure microreactor (HPMR) 384-50.

It has the capability, to ensure 384 parallel reactions up to 50 bar under ensuring of inert gas conditions in a standard laboratory environment. Heating and cooling in a range of 0–100 °C can be realized using Peltier elements. Mixing of the reaction partners is provided by a rotating permanent magnet under the reactor with coated stirring discs in the wells of the microplate. The reactions were carried out in chemical resistant microplates, which are sealed with pierce able cap mats and fixed in a special bracket.

The HPMR 50-384 enables an excellent gas exchange in the pressure tank and thus the handling of air sensitive compounds. Different commercially available catalyst components were combined under equal reaction conditions to identify the best catalyst mixture for the enantioselective hydrogenation of methyl-2-acetamido acrylate.

We could demonstrate successfully a fully automated screening of a gas reaction with 384 catalyst mixtures in solution in one microplate with very low usage on resources, like expensive chiral ligands, metal sources and educts without any cross contamination.

1. Introduction

Today the increasing globalization requires a faster development of products at lower costs combined with a reduction of the consumption of valuable resources. These requirements have a direct influence on the development of the used technologies.

The laboratories may answer with new automated parallel reaction systems, which offer more reactions per time and smaller reaction volumes. For the integration into fully automated laboratories the reaction systems have to supply standardized reaction vessels. Since the reaction systems commercially available on the market are not fully integrable into complex laboratory systems the development of a multiparallel high pressure reactor that meets all requirements was necessary.

Currently, there are various commercial reaction systems available which allow the parallel execution of gas reactions. The systems can be divided in two groups, devices with a pressure level up to 10 bar and devices with a pressure level above 10 bar.

Examples for the first group are the ASW2000 (Chemspeed), Chem-SCAN lp (HEL) and Advantage Series 3400 (Biotage) [1,2]. These systems generally use a shared gas supply and therefore do not allow an individual pressure setting per reactor. Reaction systems of the second group are usually equipped with individual pressure settings for each reaction chamber. There are, however, differences regarding the possible temperature settings (e.g. AutoPlant and MiniPlant (Chemspeed), ChemiStation (Zinsser Analytic), Endeavor system (Biotage), SPR16 (Amtec), PPR (Symyx [3]), Chem-SCAN hp (HEL), eight-fold parallel reactor (University of Rostock [4,5]), 96-fold multi reactor (Premex [6])).

Owing to their limited integration capabilities, the available reaction systems cannot really cooperate with other devices in HTS systems in a fully automated synthesis laboratory. Several systems (high pressure parallel reactor (Symyx [7,8]) work with microplates in fact; however, the systems require too many manual interventions with respect to a fully automated synthesis lab.

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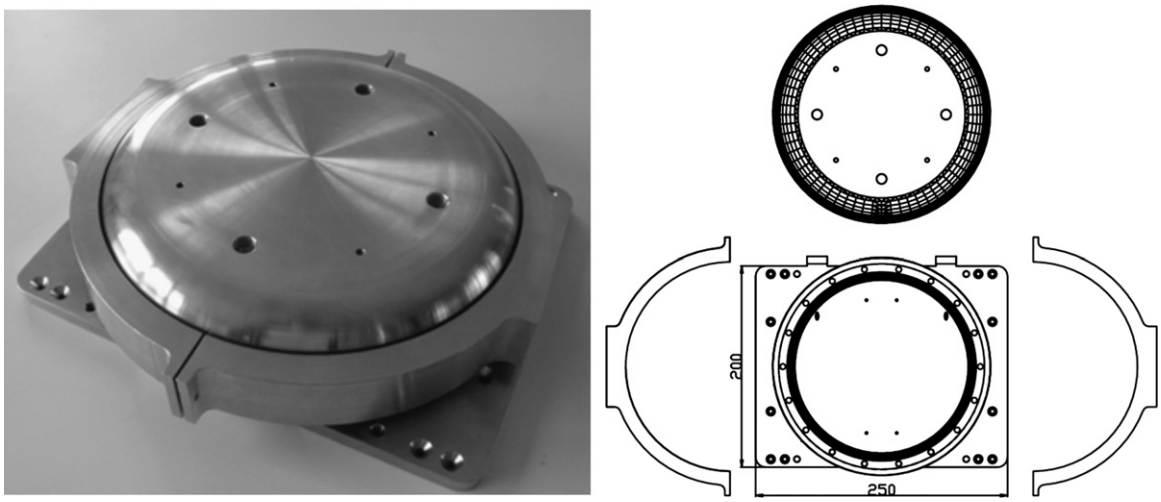

Fig. 1. Pieces of the pressure tank.

2. The reaction system

High pressure microplate reactor (HPMR) 50-384 is the further development of the HPMR 50-96 [9].

It has a pressure tank that accommodates the microplate. For setting up the reaction parameter the HPMR 50-384 includes functional units for heating, pressurization and mixing. A PC104 system is integrated for the control of the reactor. All units are positioned inside of a compact housing. The communication between the system and the operator is based on hard and software interfaces and a graphical user interface.

The pressure tank is made of a nickel based stainless steel (nickel alloy 2.4856). This alloy is nonmagnetisable, chemically stable and TÜV certificated. Furthermore, it has a high strength [10,11].

The pressure tank consists of three pieces: the lower part houses the reaction module. For the pressurization two holes for gas supply are integrated. Twelve cones are used for focussing the reaction module in the tank (Fig. 1).

The closures are required for save closing of the pressure tank. The interlocking is operated pneumatically. For safety requirements the behaviour of the construction under operating conditions was simulated (Fig. 2).

On the top of the upper part of the pressure tank, the lid, the actuators for opening and closing of the reaction module are mounted (Fig. 4). Two pneumatic cylinders generate a usable force of 367 N for moving anything in the closed pressure tank in the case of 50 bar in the tank. The lid can move horizontal with a left and right pneumatic linear drives in a distance of 100 mm. For vertical moving

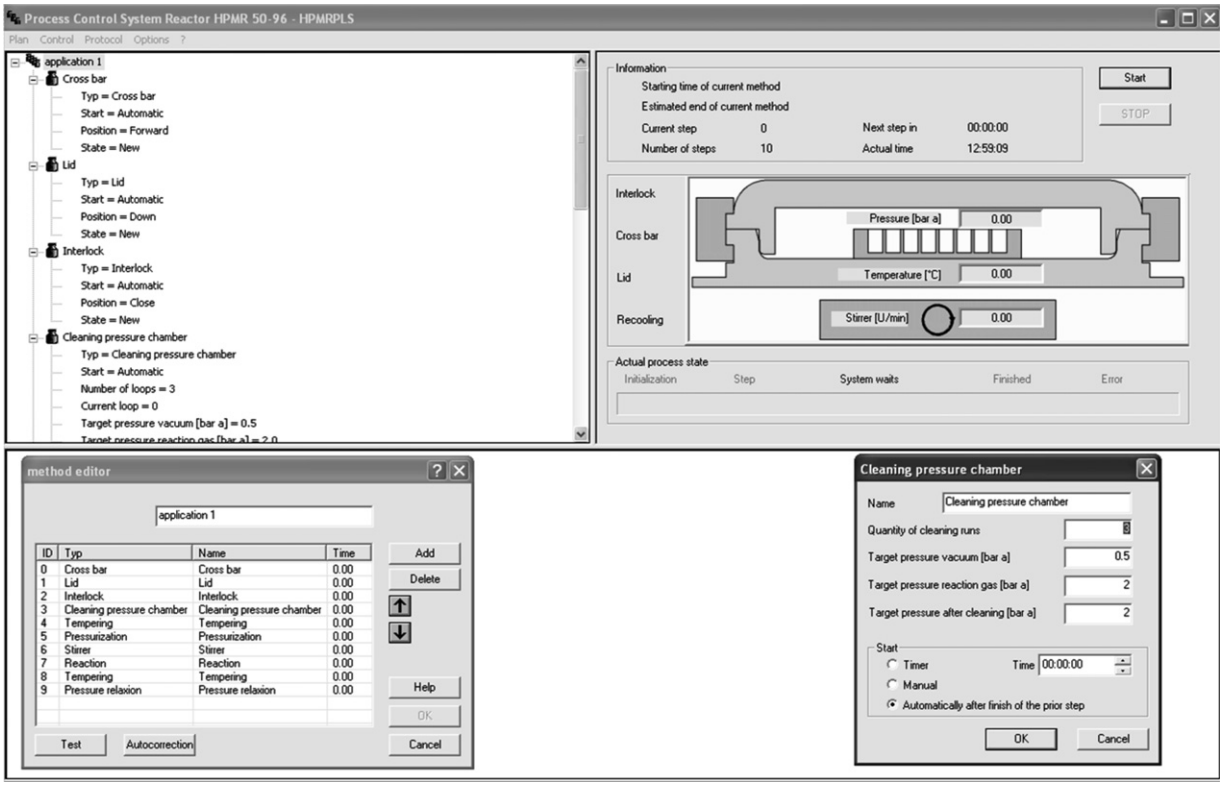

Fig. 2. Graphical user interface.

of 75 mm the lid is mounted on a further pneumatic cylinder. The gas-tight sealing of the pressure tank bases on the use of an O-ring made of Viton®, Perlast® or Kalrez® [12,13].

A tempering system based on eight robust thermo electrical coolers (TECs) used for heating and cooling the pressure tank in the range from 0 to 100 °C. TECs are heat pumps that can control the temperature by current variation. By changing the current direction the coolers are switching from heating to cooling mode. The electrical current will be controlled by two temperature controllers worked up to 50 A at 24 V. The TECs are only transporting heat from the cold site to the hot site of the element. A recooling system is used to remove the heat from the hot site of the TECs to the ambient. It contains two water coolers, one centrifugal pump and one efficient radiator. The water coolers are mounted on one side of the TECs. The cooling water is pumped via the centrifugal pump through the water coolers, warms up (in case of pressure tank cooling) and delivers the heat with the help of the radiator to the ambient air.

The second side of the TECs is mounted on the pressure tank. Due to the low heat conductivity of the pressure tank two copper plates are built-in to insure good heat transfer from the TECs to the pressure tank. With the help of the copper plates the heat transition area could be increased by the factor 4.5.

The homogenization of the reaction mixture is realized by a magnetic stirring system [14,15]. This system generates the rotation of stir discs based on the interaction with a strong magnetic cylinder, which is coupled on a gear motor. The system offers a stir velocity up to 500 rpm.

A further functional unit is the flexible gas management system for pressurization up to 50 bar. The system allows different gas exchange modes to provide among other things inert gas conditions. The central part of the gas management system is a central pressure control unit including an integrated pressure regulator with control valve. The gas flow is controlled by magnetic valves. Furthermore, the gas management system consists of non-return valves to protect the magnetic valves from reverse pressure, integrated filter to avoid contamination of the other devices of the gas management system as well as one pressure release valve and a manually useable ball valve for safety requirements.

The hardware of the HPMR 50-384 control is based on a PC104 system [16]. It includes an Intel Celeron processor with 1 GHz and 512 MB RAM. Three I/O-cards of the PC104 system offer four COM-ports, 40 optoisolated input channels and 40 relay output channels. One integrated DC/DC module supplies the PC104 system with electrical power. For data storage a 40 GB hard disk was built-in. Windows XP is used as the operating system.

All the functional units described are built-in in a compact housing from aluminium alloy profiles. The whole housing is 760 mm in width, 570 mm in depth and 670 mm in high.

The software of the control system is divided into three levels.

The first level, the local control system is used for planning, process control and process visualization. It offers interfaces to a laboratory control system and to a local operator. This first level is connected with the master level via TCP/IP.

The master operates as a supervisor of the single components and is responsible for conditioning and forwarding of the instructions to the third level, the slave level. The slave level is used for the supply of the special device functionality.

The HPMR 50-384 communicates with the operator over the graphical user interface (Fig. 2). It shows the current pressure, temperature and stirring speed rates. In addition, the progress of each method can be observed. The method planning is done through the creation of the method itself with the help of the editor. This part of the process includes the selection of the required control commands and the arrangement of its parameters within the necessary time constrains.

3. The reaction module

One of the most important components of the screening system is the reaction module, which is standardized in the SBS format [17]. Based on this feature it can be handled by a robot. The reaction module contains a 96 or 384 well microplate, a pierceable cap mat, a support frame and a perforated plate (Fig. 3). Three kinds of microplates made of polypropylene, MultiChem™ or glass can be used. The support frame and the perforated plate are made of the nonmagnetic Hastelloy C-22.

The microplate will be sealed with the cap mat positioned in the support frame in such a way, that a gas-tight sealing will result [18]. The in such way locked 384 reactors are supplied to the HPMR 50-384 under inert gas conditions, filled with the reagents and agitating stir discs.

The penetration of the cap mat is possible with the help of a gas injection system and thus a gas exchange between the pressure tank and the reaction wells can be realized (Fig. 4).

The method offers a reclosing of the reaction wells after the filling with reaction gas and thus a further process cycle under inert conditions. The opening and closing is realized with the help of two external pneumatic actuators which are installed on the lid of the pressure tank. These actuators transfer the needles of the injection system via the septa of the cap mat. For this method the renewed sealing of the plates is given by the function mode of the septa.

4. System integration

Due to its interfaces in hard- and software the described reactor can be integrated into different complex automated systems. Furthermore, the HPMR 50-384 offers a connection to a LIMS

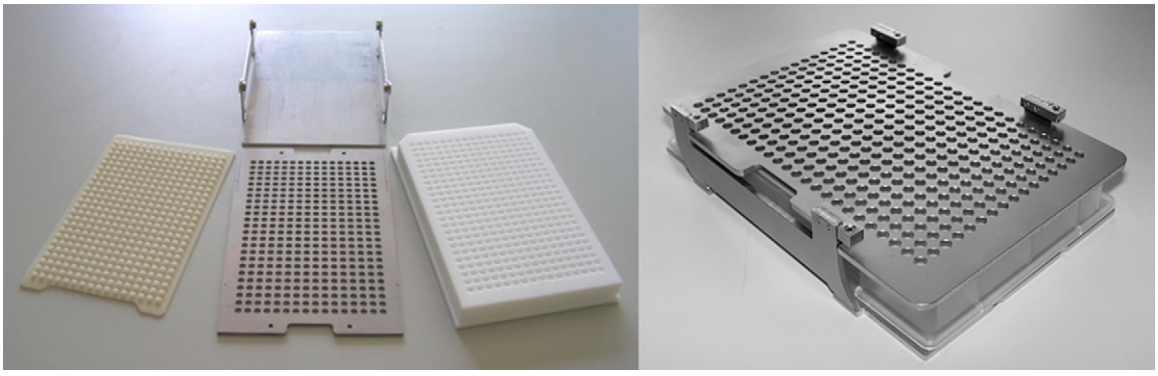

Fig. 3. Parts of the reaction module.

Fig. 4. Injection system and its actuators.

Fig. 5. Fully automated laboratory with high pressure microplate reactor, liquid handler, centrifuge and ESI-TOF-MS.

(laboratory information management system). In this case the operator can download the methods and their parameters from the reactor, change and transfer the planned method and the new parameters via an XML-Interface to the reactor [19].

Fig. 5 shows a fully automated laboratory for catalyst screening. It contains besides the microplate reactor a parallel liquid handling system for sample preparation, different plate hotels and a robot arm on a 3 m rail for the transportation of the reaction modules between the different devices. On the other side of the robot arm different analytical devices such as PAL-GC, HPLC and MS-TOF and a centrifuge have been positioned.

5. Application

The enantioselective hydrogenation of methyl-2-acetamido acrylate was chosen as an example to demonstrate the new technology. Twelve chiral ligands were combined with two special metal precursors Rh(cod)2BF4 (a) and $Rh(cod)_2SO_3CF_3$ (b) with different anions so that always 16 wells got the same mixture.

Reactions were carried out at a gas pressure of 2 bar absolute and a temperature of 25 °C for 60 min.

The stirring speed was set to 200 rpm; the working volume 40 μl/well. The substrate concentration was 0.2 mol/l, the rhodium concentration 0.2 mol% and the ligand concentration 0.21 mol% (Fig. 6).

As it is known from the literature, high enantiomeric excesses were obtained under these conditions using conventional techniques. For example, the use of the ((*S*,*S*)-Me-BPE)(COD)RhOTf complex in a 200 ml scale in a 500 ml Fisher-Porter bottle resulted in 91.4% ee and the ((*S*,*S*)-Me-DUPHOS)(COD)RhOTf complex in 99,0% ee [20]. Furthermore, it was found, that the ee-values decrease about 0.3–0.6% if the catalyst components were combined *in situ* [21]. For the experiment a microplate made of MultiChem™ material (Whatman) was used. The plate preparation was carried out manually with an Eppendorf 12 channel pipette in a glove box since many of the catalyst components are very air sensitive. Fig. 7 shows the results of the hydrogenation of acetamidometylacrylate.

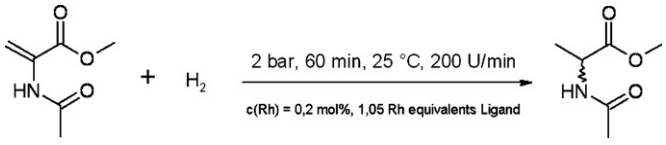

Fig. 6. Investigated reaction.

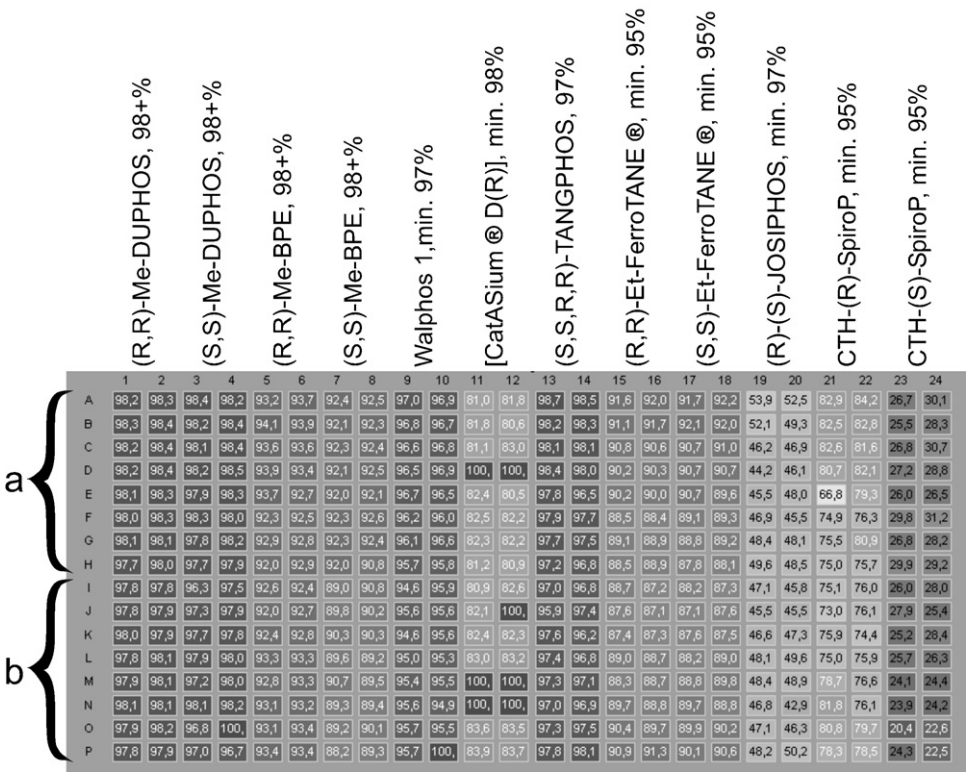

Fig. 7. ee-Values of the investigated reaction.

Table 1
Comparison of literature ee-values with experiment results

		ee (literature)	ee (found)	Relative standard deviation (%)
(*S*,*S*)-Me-BPE	$Rh(cod)_2SO_3CF_3$	91.4	89.7	0.76
(*S*,*S*)-Me-DUPHOS	$Rh(cod)_2SO_3CF_3$	99.0	97.7	0.86

Under the conditions used all mixtures except of one were converted nearly completely. Only the [catASium® D(R)] ligand showed a partial conversion of 10–20% under the used conditions.

The best results in the ee-values could be found for the *R*-isomer with the (*S*,*S*)-Me-DUPHOS ligand. For the *S*-isomer the (*R*,*R*)-Me-DUPHOS and the (*S*,*S*,*R*,*R*)-TANGPHOS ligands were the best. The worst results concerning the ee-values were detected using the CTH-(*S*)-SpiroP and (*R*)-(*S*)-JOSIPHOS ligands.

The screening results are in good accordance to the published results. As described in literature lower ee were found do to the *in situ* generation of the catalysts during the screening experiments. Table 1 summarizes the results for the two catalysts. The values listed under the column "ee found" are the results of the respective 16 parallel experiments of exactly same conditions.

A further experiment included the determination of the standard deviation of the results over 384 wells of a microplate. For this reason all wells were filled with the same reaction mixture based of the (*R*,*R*)-Me-DUPHOS ligand and Rh(cod)2BF4 as precursor. With a mean ee-value of 98.9% a relative standard deviation of 0.8% was detected.

The use of the multiparallel reactor enables a tremendous reduction of time and costs and is thus an ideal system for increasing the efficiency of chemical syntheses. The manual sequential performance would allow for four experiments per day; a total of 96 days is necessary for 384 reactions. Even with an eight-fold parallel reactor 16 days will be needed. This time saving multiplies itself by the reaction time. Furthermore downscaling of the reaction volume decreases the amount of the utilized solvents as well as often valuable starting materials and catalysts.

6. Summary

The HPMR 50-384 and its reaction modules represent a significant development in the field of reaction technology. Due to its structural set-up, its modular structure, and the design of the control software, it can be used both in stand-alone mode and as an integrated component of more complex laboratory automation systems, supported by robots. The potential applications of the reactor are in the field of catalytic high pressure reactions, synthesis optimizing and combinatorial chemistry. In combination with the several reaction modules the reactor increases the possibilities and productivity of laboratories.

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