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Application of packed-bed reactors in continuous-flow systems

PhD thesis summary

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1. INTRODUCTION

Words and phrases such as artificial intelligence, machine learning, neural networks, robotics, the cloud, big data and the internet of things are typically associated with the concept of the third industrial revolution, which is currently under way.[1] Therefore, competition at every industrial fields becoming more and more intense in terms of productivity, sustainability, profitability and speed. No exception can be made in case of the chemical industry or industrial activities with a wide range of chemical disciplines. Continuous-flow chemistry (CF) offers a solution to these challenges due to its advantages properties. Hungarian research groups have played an important role in the spread of both analytical[2] and preparative organic chemical application of this approach. Most recently H-Cube launched by Ferenc Darvas brought enormous professional and cash adventure in the field of continuous catalytic hydrogenation.[3]

One of the major benefit of CF methods is the excellent parameter control, as consequence increased reproducibility, safety and selectivity can be rationalised. In the other hand applying a CF method makes it easy to develop scalable, sustainable and economical processes.

During my PhD research, I elaborated CF methods applying packed-bed reactors (PBR) in three different research topics. We have developed a hybrid process combining a CF *Michael addition* reaction and an organic solvent nanofiltration (OSN) method for *in situ* continuous solvent and reagent recycle. In another work a new CF macrocyclization process producing crown ethers was realised through a *Williamson-type* ether synthesis. In a third topic porphyrin based biomimetic synthesis of drug metabolites have been developed in batch and CF PBRs.

2. LITERATURE REVIEW

2.1. Flow chemistry and organic solvent nanofiltration

At a first glance, the main difference between continuous production processes that have been successfully used in petrochemicals for decades and laboratory size flow chemistry, is the significantly smaller dimeter of the flow channels[4] At the same time, in such tight flow channels laminar flow becomes characteristic. This results a narrow residence time distribution, thereby contributing to excellent control of the reaction time. In addition, small diameter flow channels provides good mixing and excellent heat transfer properties for flow reactors.[5] This ensures that the reaction parameters can be maintained at a desired value, resulting increased safety, reproducibility, and a higher degree of robustness with simple scalability.[6] Moreover the use of in-line

[1] S. V. Ley *Angew. Chemie Int. Ed.*, **2018**, *57*, 5182–5183.
[2] E. Pungor, Zs. Feher, G. Nagy, K. Toth, G. Horvai, M. Gratzl *Anal.Chim.Acta.* **1979**, *109*, 1−24.
[3] Darvas, F.; Hessel, V.; Dorman, G. (Eds.) *Flow chemistry 1−2.*, De Gruyter: Berlin, Boston, **2014**.
[4] L. Vaccaro *Sustanable Flow Chemistry: Methods and Applications*; Wiley-VCH: Weinheim, **2017**.
[5] J. Wegner, S. Ceylan, A. Kirschning *Chem. Commun.* **2011**, *47*, 4583–4592.
[6] S. G. Koenig, H. F. Sneddon *Green Chem. Green Chem.*, **2017**, *19*, 1418–1419.

analytical techniques provides the opportunity to control and automate CF process.[7]

PBRs are filled columns containing randomly arranged solid reagent or catalyst particles, where the chemical reaction occurs during flow through in small diameter irregular channels of the packed-bed. Due to their simple and extensive applicability, PBR-based methods are the most general approaches for the implementation of CF heterogeneous catalysis.[8]

In a typical CF process reactants are used in dilute solutions in order to minimise the risk of clogging caused by solid precipitation. Since solvent consumption poses significant costs and environmental burden, such CF methods can only be truly sustainable if solvent recovery is employed.[9] However available subsequent downstream processing options are limited.

Organic solvent nanofiltration (OSN) could represent a solution to this problem, which is a membrane based technology that has been used for solvent recovery.[10] Among membrane operations OSN can be positioned between ultrafiltration and reverse osmosis. As it comes from their name active polymeric or ceramic layer of these membranes resistant to organic solvents and their pore diameter is in nanometre scale. This a pressure driven technique, which is capable to distinguish and separate molecules by their size in a range of 50-2000 Da. OSN thus provides the opportunity to develop new methods for continuous downstream processing resulting concentration of the product, or solvent recovery. Despite their obvious potential, attempts for the synergistic coupling of CF reactors and nanofiltration are scarce. In this context nanofiltration was used for the recovery of homogeneous catalysts[11] as well as for solvent exchange.[12]

2.2. Synthesis and selective complexing ability of pyridino-18-crown-6 ethers

Selective transformations or transport processes are found in almost every biological processes occurring in living organisms. Examples include enzyme catalysed transformations or selective transportation of ions through biological membranes. Selective complexation properties biomolecules are based on molecular recognition, in which case the host molecule selectively binds a certain type of guest molecule through noncovalent bonding. Complexes formed by the action of molecular recognition are the result of non-covalent interactions emerging between stereoelectronically complementary groups. Previously, molecular recognition was considered exclusively as a biological phenomenon, but pioneering work of *Pedersen* in the 1960s, clearly proved that it can be achieved by relatively simple synthetic molecules, such as crown

[7] Baumann, M.; Baxendale, I. R.; Ley, S. V.; Smith, C. D.; Tranmer, G. K. *Org. Lett.*, **2006**, *8*, 5231–5234.

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[9] P. Yaseneva, D. Plaza, X. Fan, K. Loponov, A. Lapkin *Catal. Today*, **2015**, *239*, 90–96

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[11] L. Cseri, T. Fodi, J. Kupai, Gy. T. Balogh, A. Garforth, Gy. Szekely *Adv. Mater. Lett.*, **2017**, *8*, 1094–1124.

[12] L.Peeva, J. Da Silva Burgal, Z. Heckenast, F. Brazy, F. Cazenave, A. Livingston, *Angew. Chemie - Int. Ed.*, **2016**, *55*, 13774–13777.

ethers.[13]

A special case of molecular recognition is the enantiomeric recognition, which represents a distinction of enantiomers of guest molecules by an enantiomerically pure host molecule. The enantiomeric recognition of chiral crown ethers was first reported by *Cram et al.* after successful separation of enantiomers of protonated primary amines.[14] Today, chiral crown ethers are widely used as artificial selector molecules due to their selective complex formation ability. One of the most attractive application of enantiopure crown ethers is immobilization on solid supports by covalent bonds and the liquid chromatographic employment of the resulting chiral stationary phases.[15] *Izatt et al.* founded that crown ethers containing a pyridine subunit show outstanding complexation properties toward protonated primary amines thanks to their aromatic ring and the nitrogen atom.[16]

Conventional synthesis of enantiopure pyridino-18- crown-6 ethers is typically a long linear procedure with a crucial macrocyclization step. This macrocyclization is a *Williamson-type* ether formation reaction, where *O*-alkylation of primary or secondary alcohols is carried out with alkyl tosylates after a deprotonation step applying NaH[17,18]. Using batch conditions this reaction takes place up to 120 hours and usually provides poor yields. Our aim was to improve the outcome of this reaction step with the help of CF methodology.

2.3. Investigation of human drug metabolism

The study of the metabolism of drug candidate molecules is one of the key issues in the drug discovery process. Identification of the major metabolites may give clues to metabolically more stable candidates. Screening for reactive metabolic intermediates would also provide useful information on how to fine-tune the lead structure to decrease the risk of side effects caused by reactive metabolites. In addition, identification of pharmacologically active metabolites is necessary for the determination of their pharmacodynamics contributions.[19] To realize the closest model for biological oxidation, traditionally the first-pass liver-specific metabolic routes of lead compounds were characterized with the aid of in vitro models that apply hepatocytes, liver microsomes, or recombinant enzymes from different species.[20] Despite their chemoselectivity, the scope of these methods to produce metabolites is limited by high costs and problems with isolation, which is due to the low substrate

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[14] L. R. Sousa,; G. D. Y. Sogah, D. H. Hoffman, D. J. Cram *Am. Chem. Soc.*, **1978**, *100*, 4569–4576.

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[17] R. M. Izatt, T.Wang, J. K. Hathaway, X. X. Zhang, J. C. Curtis, J. S. Bradshaw, C. Y. Zhu, P. Huszthy *J. Incl. Phenom. Mol. Recognit. Chem.*, **1994**, *17*, 157–175.

[18] G. Horváth, P. Huszthy *Tetrahedron: Asymmetry* **1999**, *10*, 4573–4583.

[19] A. F. Nassar *Drug Metabolism Handbook: Concepts and Applications*; A. F. Nassar, P. F. Hollenberg, J. Scatina Eds.; Wiley-VCH: New Jersey, **2009**.

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loading capacity and the complexity of the biological matrix. As a possible solution, different electrochemical and catalytic biomimetic models have been developed to produce drug metabolites more efficiently. [21] Among the many catalysts used in the in vitro biomimetic models, metalloporphyrins are recognized as one of the most efficient catalysts, because they are able to mimic cytochrome P450 isoenzyme functions owing to structural similarities with its prosthetic heme group.[22]

In such biomimetic models, oxidants, such as alkyl peroxides, peracids, sodium chlorite, sodium periodate, and iodosylarenes, are generally used to produce the active catalytic species from the iron(III) porphyrin through a "peroxo shunt".[23] The chemical nature of the activated species depends on the structure of the metalloporphyrins, the oxidant, and the reaction conditions, particularly the reaction media.[24] Consequently, it is possible to fine-tune the distribution of the different activated species of the metalloporphyrin catalysts to achieve different enzyme mimetic reactivity. Application of these model systems to drug molecules under a variety of reaction conditions allows the preparation and isolation of metabolites in sufficient quantities for structural elucidation. However, the absence of the protein environment could result in lower regioselectivity and decreased stability of the synthetic metalloporphyrins compared with the heme enzymes, [25] which would be due to the lack of selective orientation of the substrate molecules relative to the oxo–iron species and stabilization of the activated iron centre.

Degradation of metalloporphyrin catalysts can be another critical issue in these model systems. This may involve either mono- or bimolecular self-destruction, which is induced by an excess of the oxidizing agents[26] and/or free radicals that are formed in the metalloporphyrin-catalysed reactions.[27] Attempts to improve the catalyst stability, which included ortho substitution of the phenyl rings of tetraaryl porphyrins with bulky groups or introduction of electron-withdrawing substituents to metalloporphyrins, led to increased resistance. Immobilization of metalloporphyrins on suitable supports through physical entrapment, covalent binding, or surface adsorption onto solid carriers can also give increased stability against degradation by inhibiting bimolecular self-destruction and through inactivation by μ-dimer formation under neutral and basic conditions.[28] Furthermore, the application of immobilized catalysts offers the advantage of both catalyst separation and recycling.

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[28] M. J. Nappa, C. A.Tolman *Inorg. Chem.*, **1985**, *24*, 4711–4719.

3. EXPERIMENTAL METHODS

During the synthesis of the compounds the well-established methods of preparative organic chemistry were used. The progress of reactions was followed by TLC, TLC-MS and HPLC-MS techniques. During the medium-throughput screening (MTS) biomimetic oxidation experiments 96 well plates were used in HPLC or HPLC-MS. The crude products were purified by column chromatography, preparative thin layer chromatography or preparative HPLC. Structures of the products were determined using, ^{1}H- and ^{13}C-NMR and HRMS spectroscopies.

During the CF experiments syringe or HPLC pumps were used. Polytetrafluoroethylene (PTFE) or stainless steel tubing (with 1/16″ outer diameter, 0.02″ inner diameter), flangeless polyetheretherketone (PEEK) fittings with PEEK ferrules, and PEEK union (0.02″ inner diameter) were used in conjunctions. As PBRs glass columns with adjustable column end pieces or stainless steal columns were used.

Membrane tests and membrane separation were performed using a custom-made membrane module, and commercially available membranes with one exception. The polybenzimidazole (PBI) membrane was prepared by membrane casting method using a PBI stock solution (26 m/m%) in *N*,*N*-dimethylacetamide containing LiCl stabilizer (1,5 m/m) and a polypropylene non-woven support layer.

The structure of the polymer-bound bases was investigated before and after use by FTIR spectroscopy.

The supported porphyrin catalysts were characterized by Scanning Electron Microscopy with Energy Dispersive X-Ray Analysis (SEM-EDAX) and inductively coupled plasma/optical emission spectroscopy (ICP-OES) measurements.

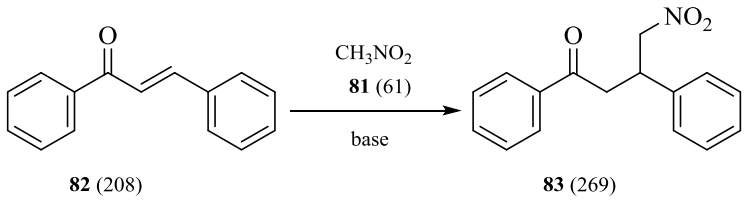
4. RESULTS

4.1 Nanofiltration-enabled solvent and reagent recycle [I.]

Solvent usage in the pharmaceutical sector accounts for as much as 90% of the overall mass during manufacturing processes. Consequently, solvent consumption poses significant costs and environmental burdens. Continuous processing, in particular continuous-flow reactors, have great potential for the sustainable production of pharmaceuticals but subsequent downstream processing remains challenging. Herein the development of a nanofiltration-enabled in situ solvent and reagent recycling process to improve the sustainability of flow reactors is presented.

Michael-addition of nitromethane to *trans*-chalcone was selected as a model reaction (*Scheme 1.*). Optimization of the parameters (solvent, temperature, catalyst, excess of reagent and residence time) of the model reaction resulted full conversion of the starting material to the desired product applying. Therefore, the outflow contained only the product and the excess of nitromethane in acetone.

During the optimization of the membrane separation, we determined the most effective retention parameters (membrane quality, pressure, retentate/permeate ratio) giving acceptable flux. Based on these studies, the commercially available Duramem150 polymer membrane was selected for further studies.



Scheme 1. Michael Addition of nitromethane reagent to *trans*-chalcone substrate catalysed by polymer-supported trialkylamine base. The molecular weights (in g/mol) are given in parentheses for each compound.

By coupling the PBR and the OSN module, the reagent excess and the solvent was recycled (after the equilibrium concentrations have been reached) (*Figure 1.*). On the retentate side of the membrane, the high molecular weight product remained at an increased concentration while the small molecule solvent and reagent passed through the membrane, which allowed them to be recycled. The hybrid process was operated continuously over six weeks, recycling about 90% of the solvent and reagent. Consequently, the E-factor and the carbon footprint were reduced by 91% and 19%, respectively.

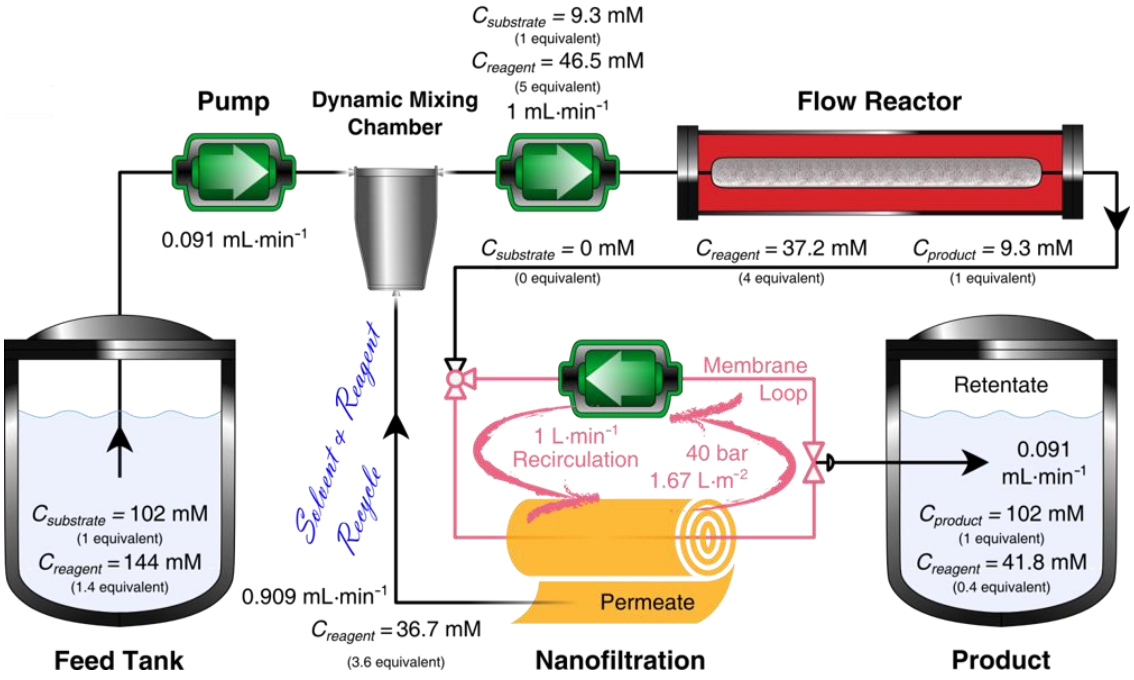


Figure 1. Experimental setup of the hybrid system applying solvent and excess of reagent recycle.

4.2. Application of flow chemistry to macrocyclization of pyridino-18-crown-6 ethers [II.]

As the functionalized crown ethers are key intermediates of the crown ether-based CSPs, there is an obvious need for improved material availability with lower production cost and in more reproducible way. Preparation of crown ethers **38**−(*S*,*S*)-**47** (*Figure 2.*) in batch mode is already published.[29] In this study we developed a new continuous-flow method to implement macrocyclization of crown ethers. To achieve this goal, it was necessary to replace the tosylate leaving groups with a more soluble iodine leaving groups in order to avoid clogging of the PBR.

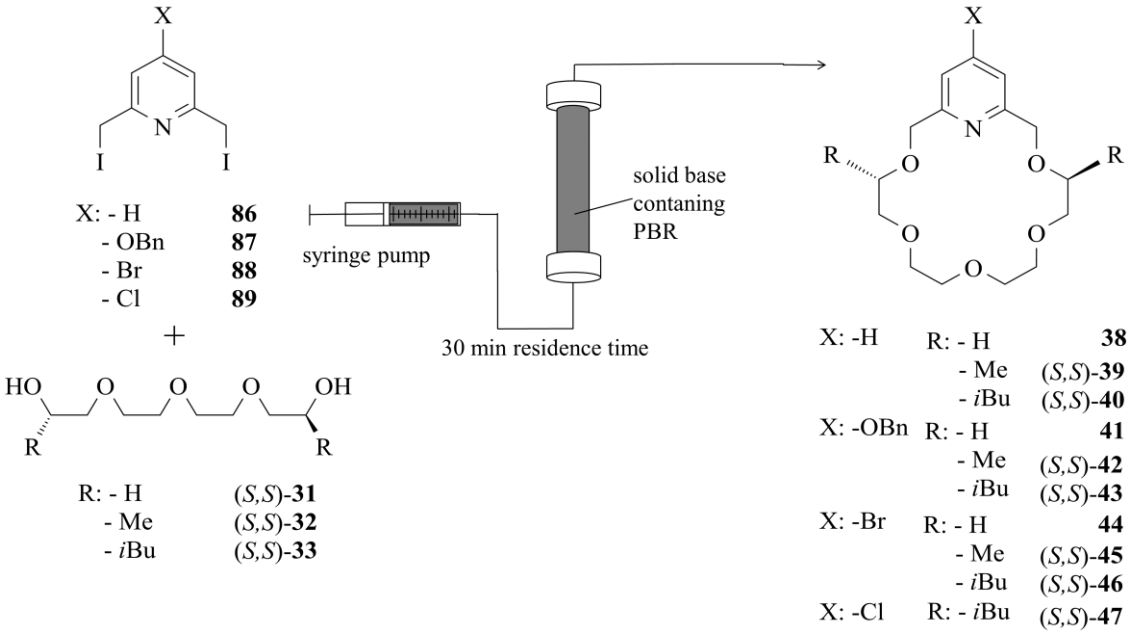


Figure 2. Experimental setup for macrocyclization of pyridine-18-crown-6 ethers in a packed-bed reactor.

Macrocyclization have been performed in a packed-bed flow reactor where deprotonation of a bifunctional primary or a secondary alcohol takes place with potassium hydroxide as a heterogeneous base avoiding the use of stronger and more dangerous one, sodium hydride. The optimization of the parameters provided higher yields in significantly shorter reaction times (30 min) (*Table 1.*). The setup presented here is suitable for the preparation of different ethers by *Williamson-type* syntheses in continuous-flow reactions.

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Table 1. Comparison of previously reported and achieved yields and reaction times in macrocyclization of crown ethers [**38**−(*S*,*S*)-**47**].

Enry	Compound	X	R	Flow yield[a] (%)	Batch yield[b] (%)	Reaction time[c] (h)
1	**38**	H	H	81	55	3
2	(*S*,*S*)-**39**	H	Me	88	56	48
3	(*S*,*S*)-**40**	H	*i*Bu	82	45	96
4	**41**	OBn	H	63	47	120
5	(*S*,*S*)-**42**	OBn	Me	74	34	17
6	(*S*,*S*)-**43**	OBn	*i*Bu	69	21	96
7	**44**	Br	H	39	32	16
8	(*S*,*S*)-**45**	Br	Me	34	8	48
9	(*S*,*S*)-**46**	Br	*i*Bu	33	12	48
10	(*S*,*S*)-**47**	Cl	*i*Bu	76	13	48
11[d]	(*S*,*S*)-**42**	OBn	Me	−	76[a]	24

[a] *Yields of crown ethers were determined by HPLC. 30 min residence time.*
[b] *Reported isolated yields.*
[c] *Reaction times reported in the literature.*
[d] *Comparative batch reaction:*

4.3. Separation studies of pyridino-18-crown-6 ether based chiral stationary phase [III.]

In our research group, the (*S*,*S*)-CSP-**54** chiral stationary phase containing (*S*,*S*)-**42** selector unit was successfully synthesized and tested in a separation of a small number of chiral aralkyl amines (*Figure 3.*).[30]

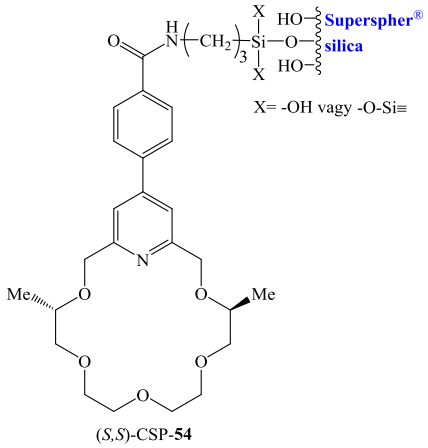


Figure 3. Az (*S*,*S*)-CSP-**54** királis állófázis szerkezete.

In the course of our work, the range of analytes tested was extended with three additional aromatic primary amines and six amino acid esters.The enantiomeric discrimination of chiral stationary phase (*S*,*S*)-CSP-**54** was evaluated by HPLC using the mixtures of enantiomers of various protonated primary aralkylamines [1-phenylethylamine hydrogen perchlorate (PEA), 2,3-dihydro-1H-inden-1-amine (1-aminoindan), 2,2'-(1,2-diaminoethane-1,2-diyl) diphenol (HPEN)] and perchlorate salts

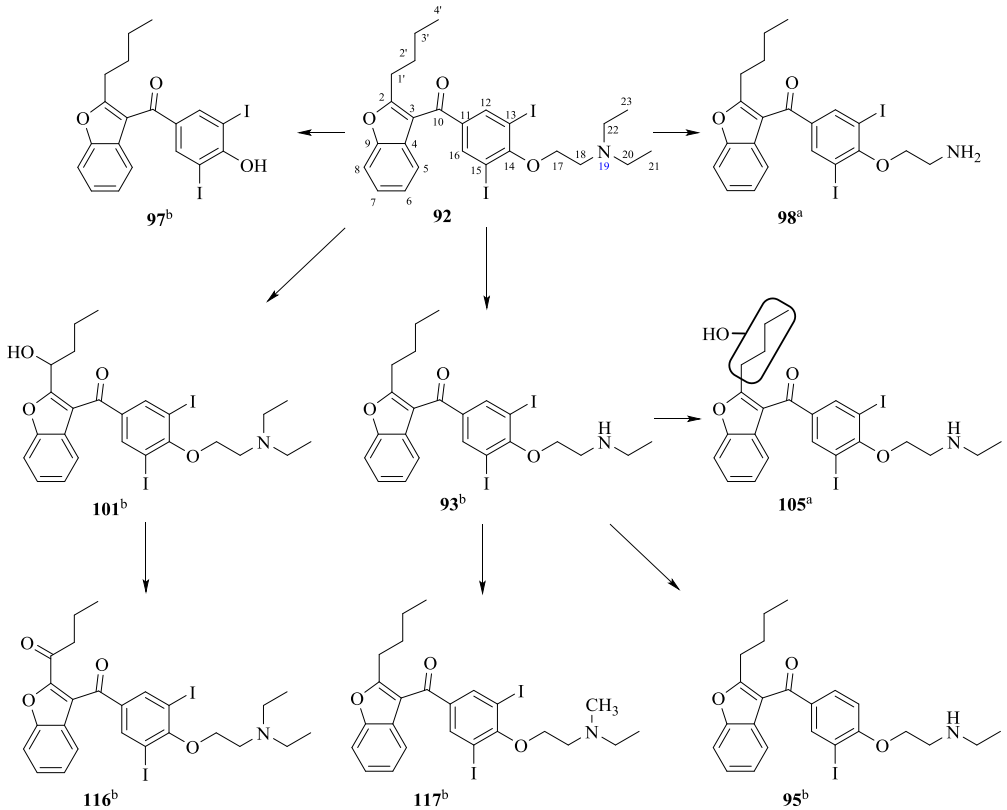
[30] J. Kupai, S. Lévai, K. Antal, Gy. T. Balogh, T. Tóth, P. Huszthy *Tetrahedron: Asymmetry* **2012**, *23*, 415–427.

of α-amino acid esters [alanine benzyl ester (Ala-OBn), phenylalanine benzyl ester (Phe-OBn), phenylalanine methyl ester (Phe-OMe), phenylglycine methyl ester (PhGly-OMe), glutamic acid dibenzyl ester (Glu-diOBn), and valine benzyl ester (Val-OBn)]. The best enantioseparation was achieved in the case of PEA. The high enantioselectivity was rationalized by the strong π–π interaction of the extended π system of the aryl-substituted pyridine unit.

4.4. Biomimetic synthesis of drug metabolites in batch and continuous-flow reactors [IV.]

A medium-throughput screening (MTS) of biomimetic drug metabolite synthesis is developed by using an iron porphyrin 5,10,15,20-tetrakis(4-sulfonatophenyl)porphyrin iron(III) chloride (FeTSPP) catalyst. The microplate method, in combination with HPLC-MS analysis, was shown to be a useful tool for process development and parameter optimization in the production of targeted metabolites and/or oxidation products of forty-three different drug substances. Application of different compositions of MeOH/aqueous buffer in a pH range of 2.75−7.4 mixture (4:1, v/v) and *t*BuOOH, H_2O_2, or $NaIO_4$ as oxidants provided changes in reactivity.

Amiodarone (**92**) was considered as a suitable test compound as it is a well-known drug molecule and its comprehensive metabolism studies, mediated by CYP450 isoenzymes, are available. Oxidized products shown in *Scheme 2.* and *Table 2.* were isolated in an amount sufficient for exact structure determination after scaling-up batch biomimetic reactions.



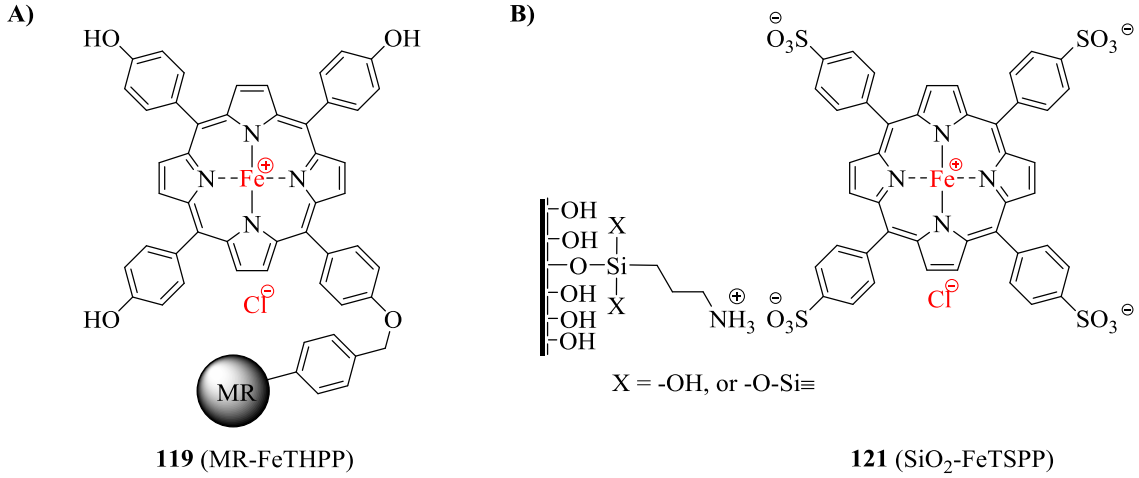
Scheme 2. Structures and numbering of amiodarone (**92**) and its oxidized products obtained in biomimetic oxidations. [a] Structures were suggested by HRMS or [b] HRMS and NMR spectroscopy.

Table 2. Relative product distributions (HPLC-DAD area%) in biomimetic oxidations of amiodarone (**92**) by using *t*BuOOH, H_2O_2, and $NaIO_4$ at various pH values.

Meta-bolite	Oxidant																	
	*t*BuOOH						H_2O_2						$NaIO_4$					
	pH																	
	2.75	3.6	4.0	4.5	5.0	5.6	2.75	3.6	4.0	4.5	5.0	5.6	2.75	3.6	4.0	4.5	5.0	5.6
93[a]	–	14	29	67	78	78	3	38	52	60	62	49	20	68	65	56	29	19
95[a]	–	–	3	10	10	8	–	–	1	1	1	1	–	–	1	1	–	–
97[a]	–	–	–	–	–	–	–	4	10	18	19	19	–	–	–	–	–	–
98[a]	–	–	–	–	–	–	–	–	–	–	–	–	4	4	6	10	9	7
101[b]	17	7	3	–	–	–	–	–	–	–	–	–	1	–	–	–	–	–
105[a]	–	4	4	1	–	–	–	–	–	–	–	–	1	3	2	3	3	1
116[b]	20	19	10	–	–	–	–	–	–	–	1	–	–	–	–	–	–	–
117[b]	2	11	14	8	1	–	–	–	–	–	–	–	1	4	5	7	11	10
92	41	31	23	4	1	1	91	47	25	9	1	16	64	–	–	–	–	–
Other	20	13	14	9	10	11	3	10	11	12	16	15	8	20	21	24	48	62

[a] Known metabolite of compound of **92**. [b] Biomimetic oxidation product of compound of **92**.

Fast degradation and poor recovery of the porphyrin catalysts under batch conditions was overcome by immobilization of the metalloporphyrins on the surface of *Merrifield-resin* and 3-aminopropyl-functionalized silica (*Figure 4.*). The supported catalyst was successfully applied in a packed-bed reactor under continuous-flow reaction conditions for the large-scale synthesis of amiodarone (**92**) metabolites. In terms of the production of **93** *N*-desethyl amiodarone, the major metabolite observed in the human body, **121** supported porphyrin proved to be more effective in achieving a 92.3 mg/day yield and a 74% overall conversion.



119 (MR-FeTHPP) **121** (SiO_2-FeTSPP)

Figure 4. Structure of **A**) **119** *Merrifieled*-resin- and **B**) **121** 3-aminopropyl-functionalized silica supported porphyrin catalysts.

5. THESES

1. We elaborated a new nanofiltration-enabled in situ solvent and reagent recycling process to improve the sustainability of flow reactors. The efficiency of the hybrid process was experimentally confirmed by six weeks' continuous operation, leading to the recovery of about 90% of the solvent and the excess of the reagent. Consequently, the E-factor and the carbon footprint were reduced by 91% and 19%, respectively. [I]

2. Nitromethane-induced degradation of the trialkylamine base catalysts during the continuous flow *Michael addition* has been experimentally confirmed. We proved that replacing the initially applied polymer containing dialkylbenzylamine groups with a polymer containing trialkylamine groups without benzyl carbon atoms, the rate of catalyst deactivation could significantly be reduced. [I]

3. We worked out a new continuous-flow method applying a packed-bed reactor for macrocyclization of achiral and chiral pyridino-18-crown-6 ethers. We proved that, replacement of the ditosylate derivatives of pyridine as precursors for the macrocyclization used in batch condition by the appropriate diiodides could avoid formation of solid precipitation. It was found deprotonation of a bifunctional primary or a secondary alcohol took place with potassium hydroxide as a heterogeneous base avoiding the use of stronger and more dangerous one, sodium hydride. Optimization of the reaction parameters provided crown ethers in higher yields and shorter reaction times compared to the already reported values. We proved that our setup is suitable for the preparation of different ethers by *Williamson-type* syntheses in continuous-flow reactions. [II]

4. By high performance liquid chromatography (HPLC) studies, we proved that the enantiopure pyridino-18-crown-6 ether-based CSP attached through an aryl moiety was appropriate to separate the enantiomers of protonated primary aralkylamines and perchlorate salts of α-amino acid esters. [III]

5. We elaborated a new biomimetic method applying solid supported porphyrin catalysts in packed-bed reactors for synthesis of drug metabolites. Using this

method, direct synthesis of the major human metabolite of amiodarone drug was achieved with higher productivity compared to a homogeneous batch experiment with the same stoichiometry. [IV]

6. A medium-throughput screening (MTS) method for biomimetic drug metabolite synthesis was developed by using an iron porphyrin catalyst. We proved that the microplate-based method, in combination with HPLC-MS analysis, is a useful tool for process development and parameter optimization in the production of targeted metabolites and/or oxidation products. In the case of scaled-up biomimetic oxidations the high quantity and purity of the isolated products enabled detailed HRMS and NMR spectroscopic studies for structural elucidation. [IV]

6. POSSIBLE APPLICATIONS

Effective, robust and well-controlled CF synthesis is of great interest in the pharmaceutical- and fine chemical industries. As an in-line downstream process, our reagent and solvent recycling method, can greatly increase the sustainability of CF synthesis.

The development of an efficient, CF macrocyclization of pyridine-18-crown-6 ethers enables significant cost saving in the production of pyridino-crown ether based chiral phases. Furthermore, our method is suitable for the continuous synthesis of other ethers.

Our porphyrin-based oxidation system, which allows direct synthesis of metabolites of drug substances, has been successfully applied in many cases to predict the metabolism of drug candidate molecules at Gedeon Richter Plc. Therefore, further pharmaceutical utilization of this method is expected in the future.

7. PUBLICATIONS

7.1. Publications related to the dissertation

I. **T. Fődi,** C. Didaskalou, J. Kupai, Gy. T. Balogh, P. Huszthy, Gy. Szekely: Nanofiltration-Enabled *In Situ* Solvent and Reagent Recycle for Sustainable Continuous-Flow Synthesis, *ChemSusChem* **2017**, *10*, 3435−3444.
[IF: 7.411; C: 30]

II. **T. Fődi,** J. Kupai, Gy. Túrós, T. Németh, E. Rojik, E. Riethmüller, Gy. T. Balogh; P. Huszthy: Application of flow chemistry to macrocyclization of crown ethers *J. Flow. Chem.* **2016**, *6*, 279–301.
[IF: 1.768; C: 0]

III. S. Lévai, T. Németh, **T. Fődi,** J. Kupai, T. Tóth, P. Huszthy, Gy. T. Balogh: Studies of a pyridino-crown ether-based chiral stationary phase on the enantioseparation of biogenic chiral aralkylamines and α-amino acid esters by high-performance liquid chromatography, *J. Pharm. Biomed. Anal.* **2015**, *115*, 192–195.
[IF: 3.169; C: 7]

IV. **T. Fődi,** G. Ignácz, B. Decsi, Z. Béni, Gy. I. Túrós, J. Kupai, D. Balogh-Weiser, I. Greiner, P. Huszthy, Gy. T. Balogh: Biomimetic Synthesis of Drug Metabolites in Batch and Continuous-Flow Reactors, *Chem. Eur. J.* **2018**, *24*, 9385−9392.
[IF: 5.16; C: 0]

7.2 Further publications

V. A. Kormos, A. Sveiczer, **T. Fődi**, Á. Rohonczi, P. Huszthy: Synthesis of novel 18-crown-6 type ligands containing a phenothiazine 5,5-dioxide unit, *Arkivoc* **2013**, (*iv*), 227–239.
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VI. T. Németh, S. Lévai, **T. Fődi**, J. Kupai, Gy. Túrós, T. Tóth, P. Huszthy, Gy. T. Balogh: A Novel Method for the Preparation of a Chiral Stationary Phase Containing an Enantiopure Acridino-18-Crown-6 Ether Selector, *J. Chromatogr. Sci.* **2015**, *53*, 431–435.
[IF: 1.320; C: 1]

VII. L. Cseri, **T. Fődi**, J. Kupai, Gy. T. Balogh, A. Garforth, Gy. Szekely: Membrane-assisted catalysis in organic media, *Adv. Mat. Lett.* **2017**, *8*, 1094−1124.
[IF(2014): 1.460; C: 5]

7.3 Oral presentations related to the dissertation:

VIII. **T. Fődi**, G. Ignácz, J. Kupai, G. T. Balogh, P. Huszthy: Application of synthetic metalloporphyrins in biomimetic oxidation of drugs, *MTA Heterociklusos és Elemorganikus Munkabizottság Ülése*, Balatonszemes, **2017**.

IX. **T. Fődi**, C. Didaskalou, J. Kupai, G. T. Balogh, P. Huszthy, G. Szekely: Membrane assisted continuous-flow reactions, *6th European Young Engineers Conference*, Warsaw, **2017**.

X. **T. Fődi**, J. Kupai, G. Túrós, G. T. Balogh, P. Huszthy: Flow chemistry in macrocyclization of crown ethers, *5th European Young Engineers Conference*, Warsaw, **2016**.

XI. **T. Fődi**, M. Katz, J. Kupai, T. Tóth, Gy. T. Balogh, P. Huszthy: Synthesis of new pyridine-18-crown-6 ether based stationary phase precursors, *MTA Szteroid és Terpenoidkémiai Munkabizottság ülése*, Szeged, **2014**.

XII. **T. Fődi**, J. Kupai, S. Lévai, T. Németh, Gy. T. Balogh, P. Huszthy: Synthesis of new pyridine-18-crown-6 ether based statationary phase and investigation of it's enantiomeric recognition ability compared to other chiral crown ether based stationary phases, *XX. Nemzetközi Vegyészkonferencia*, Cluj-Napoca, **2014**.