Final Program & Book of Abstracts
7th Conference on Frontiers in Organic Synthesis Technology
Final Program & Book of Abstracts
16-18 October 2019, Budapest, Hungary


The professional and grammatical level of the materials is the authors’ responsibility.

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General Information

The Conference is held at the
ENSANA Thermal Margaret Island
Health Spa Hotel
between 16-18 October 2019

Address:
Margitsziget (Margaret Island),
H-1007 Budapest, Hungary

The Conference venue can be accessed by bus number 26 departing from Western (Nyugati) Railway Station, from downtown.

Technical Organiser

Diamond Congress Ltd.
1255 Budapest, P.O. Box 48.
Tel: +36 1 225-0209
http://www.diamond-congress.hu/

Opening Hours of the Registration

Wednesday, 16 October 2019  -  12:00 – 18:00
Thursday, 17 October 2019  -  08:00 – 17:00
Friday, 18 October 2019  -  08:00 – 13:00

Onsite Contact Numbers

Mr. Attila Varga
+36 20 936-2969
Diamond Congress Ltd.

Official Language

Official language of the Conference is English (no translation is available).

Badges

All participants will receive a personal badge upon registration. Delegates are kindly requested to wear their name badge when attending the meetings or social events.
Accommodation

Conference participants who arranged their reservation in advance at the venue hotel may occupy the rooms from 14:00 on the day of arrival and should arrange the check out until 10:00. The hotel ensures a luggage room. Guests are kindly requested to settle their extra room bills (such as phone calls, drinks and minibar) prior to departure.

Car Parking

Parking places are available in the parking lot, located in front of the hotel. Barrier-controlled car parking next to the hotel costs EUR 8/day. Guarded underground car park in the hotel is available for EUR 13/day.

Please choose the HOTEL button at the entrance to the Margaret Island to be able to get the above mentioned reduced prices.

Payment, Invoices

The price of the ordered services will be indicated on the final invoice according to the Hungarian official financial rules. Official final invoices and receipts for fees paid by the participants will be handed over on site at the registration desk. Please forward them to the financial department of your institution.

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The organisers cannot accept liability for any personal accidents, loss of belongings or damage to private property of participants and accompanying persons that may occur during the Conference.

Internet Access

As a courtesy to all delegates, free WiFi is available within the building for your own devices. The name of the network is Danubius_free. Password: danubius40
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          Flow Reaction Calorimetry and Process Spectroscopy: Modern Tools for
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New Frontiers in Flow Technology and Reaction Processes

Aaron B. Beeler

Boston University, Boston MA, United States
E-mail: beelera@bu.edu

Introduction

In the Beeler Research Group, we are developing new technologies and approaches that can be applied to natural product synthesis and medicinal chemistry. The lecture will highlight developments in challenging reactions which can be used to access complex small molecules which are critical in our multidisciplinary and collaborative research. A common theme in our lab is the use of flow chemistry to develop efficient reactions and processes that overcome limiting boundaries that are prevalent in batch reactions. Flow chemistry allows us to reconsider the utility of many transformations for applications in synthesis, such as photochemical reactions to access complex cyclobutanes, reactions of diazo compounds to access structurally and stereochemically diverse cycloheptatriene, and platforms to facilitate chemical synthesis in space. Ultimately, I hope to demonstrate how flow chemistry provides us a tool for development of new and more efficient reactions that are robust, highly scalable, and provide access to complex and novel chemotypes.

References


Keywords: Flow synthesis, Space chemistry,
A recent survey found that not only had more than 85% of chemists failed to reproduce a published procedure, 60% had failed to reproduce their own. While the majority of scientific disciplines rely on the availability of instrumentation, chemistry is traditionally performed in standardized and widely available glass batch reactors. This is a distinct advantage, as researchers from a breadth of economic backgrounds can study chemical transformations, perform syntheses, and be scientifically competitive. However, this approach to chemistry gives the field a unique limitation as compared to other disciplines; it is highly reliant on the physical skills of the researcher. So while this means chemistry as a discipline is accessible to researchers worldwide, there is often a large degree of variance in the results of those experiments, leading to this reproducibility problem in the field.

Issues with respect to reproducibility can be reduced via automation of flow chemical reactors. Automation has the additional advantage of greatly increasing the rate with which individual chemical processes can be studied/developed, however these instruments are only available in a few, isolated laboratories – limiting worldwide participation.

The development of chemistry remains a labor intensive process fueled by intuition and trial-and-error. In this talk, we will discuss the progress my group has made in the development of remotely accessible automated flow platforms for the standardized production of chemical data. Our work to-date culminates with the development of the radial synthesizer, capable of single and multistep reactions, and is the first instrument which does not require manual reconfiguration of the instrument between experiments. Taking advantage of the lack of equipment redundancies in iterative synthesizers and the versatility exhibited by synthesizers using a linear series of reactors, we have achieved several multi-step linear and convergent syntheses as well as generating a library of derivative structures using both thermal and photochemistry. This work will be showcased in the presentation.
Valorization of Carbon-Dioxide via Continuous-flow Electrolysis

Csaba Janáky¹, Balázs Endrődi¹, Dorottyia Hursán¹, Egon Kecsenovity¹, Richard Jones², Antal Danyi²

¹ University of Szeged, Department of Physical Chemistry and Materials Science, Szeged, Hungary
² ThalesNano Zrt., Budapest, Hungary
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Electrochemical reduction of CO₂ is a promising method for converting a greenhouse gas into value-added products, utilizing renewable energy. Novel catalysts, electrode assemblies, and cell configurations are all necessary to achieve economically appealing performance. Depending on the nature of the above components various gas and liquid phase products can be formed, laying down the basis of a more sustainable chemical industry. In this talk, I am going to talk about two of these aspects, targeted by our laboratory.

First, I am going to present a zero gap electrolyzer cell, which converts gas phase CO₂ to products without the need for any liquid catholyte. This is the first report of a CO₂ electrolyzer cell, where multiple stacks are connected, thus scaling up the electrolysis process.¹ The operation of the cell was validated using both silver nanoparticle and copper nanocube catalysts, and the first was employed for the optimization of the electrolysis conditions. Upon this, CO formation with partial current densities above 250 mA cm⁻² were achieved routinely, which was further increased to 300 mA cm⁻² (with ~95 % Faradaic efficiency) by pressurizing the CO₂ inlet. Evenly distributing the CO₂ gas among the stacks (parallel connection), the operation of the multi-stack cell was identical to the sum of multiple single-stack cells. When passing the CO₂ gas through the stacks one after the other (serial gas connection), the CO₂ conversion efficiency was increased remarkably. Importantly, the presented electrolyzer simultaneously provides high partial current density, low cell voltage (~3.0 V), high conversion efficiency (up to 40 %), and high selectivity for CO production; while operating at up to 10 bar differential pressure.

In the second part of my presentation I will shed light on the importance of catalyst morphology, using N-doped carbon (N–C) catalysts as a model system.² We found that CO₂R activity, selectivity, and stability of N–C electrodes are highly dependent on their porosity. The presence of mesopores was demonstrated to be beneficial in achieving high CO selectivity and current density, with an optimal pore size around 27 nm. Even after convoluting factors other than morphology (e.g., surface chemistry, level of graphitization, surface area), the reasons behind the observed trends are complex. CO₂ adsorption properties, wetting characteristics, and geometric effects are jointly responsible for the massive difference in the CO₂R performance. All these properties must be taken into consideration when we aim to understand the reduction mechanism on different catalysts and while improving the performance further to a technologically relevant level (as alternatives to precious metal catalysts).
References


Keywords: electrosynthesis, ethylene, syngas, solar energy conversion
The use of electrochemistry for the generation of reactive intermediates can have major advantages towards conventional synthetic strategies.\textsuperscript{[1]} Less or no reagent waste is generated and new reaction pathways are accessible.\textsuperscript{[2]} In order to exploit the electricity driven conversions for synthetic purposes and to install unique selectivity two modern approaches will be outlined:

1) Solvent-controlled selective dehydrogenative cross-coupling reactions: A key for this is the use of boron-doped diamond anodes and fluorinated alcohols within the electrolyte.\textsuperscript{[3]} This methodology opened new pathways for innovative and scalable arylation reactions.\textsuperscript{[4]}

2) New electrode systems for the anodic and cathodic conversion to value-added organic compounds. These systems are capable to go beyond common limits in electro-organic synthesis.

The working horse to identify suitable electrolytic conditions is the electrosynthetic screening approach. This strategy gives also rise to fast optimization and subsequent scale-up.\textsuperscript{[5]}

References


Keywords: electrosynthesis, dehydrogenative coupling, flow electrolysis
The Chemputer: A Universal Programmable Chemical Synthesis Robot

Greig Chisholm and Leroy Cronin*

School of Chemistry, University of Glasgow, Glasgow, United Kingdom
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Introduction

Much of chemical synthesis must be done manually as automation is limited to single classes of reactions, or work-flows. To address this, we developed an abstraction of organic synthesis which allows a universal connection between the conceptual steps and automation of the process [1-2]. These steps were implemented in a modular robotic platform, running a chemical programming language which formalizes and controls the assembly of the molecules, see Fig. 1.

Results

We validated and demonstrated the concept by making three pharmaceutical compounds and doing over ten different classes of reactions without any physical intervention. Execution was demonstrated by the fully autonomous synthesis of the pharmaceuticals, Nytol, Rufinamide, and Sildenafil and the biological chemistry reagent NHS-diazirine, with yields and purities of products and intermediates comparable or better to those achieved manually. The syntheses are captured as digital code that can be transferred flexibly between platform instances with no modification, published and versioned, thereby greatly enhancing reproducibility and reliable access to complex molecules.
References


Keywords: Automation, digitization, Chemputer, pharmaceutical, platform
Organic electrochemistry enables a broad variety of reactions, and electrochemical transformations in general have the potential to replace traditional catalytically activated reactions for e.g. heterocycle synthesis [1]. At the same time, new developments in small-scale flow reactors have increasingly gained attention as convenient tools for more efficient syntheses compared to traditional batch procedures [2]. Small-scale flow reactors provide uniform residence times, well-defined flow patterns, and precise temperature control. Their advantage for electrochemical reactions in particular is their large surface to volume ratio and the reduced ohmic resistance. This minimizes supporting electrolyte requirements so that less purification steps are required and enables green chemistry [2].

However, one of the challenges that needs to be overcome to establish continuous micro-scale electrochemical reactors is that due to their prevailing laminar flow profile, species transport, which occurs normal to the flow direction between the electrodes, is rather slow. This drastically limits the achievable throughput of electrochemical microreactors.

In this contribution, we will present the design of an electrochemical reactor with integrated ultrasound actuators. The acoustic irradiation will lead to a synergistic effect which increases species transport between the electrodes via acoustic streaming. To guide the efficient design and integration of the piezoelectric actuators, we developed an analytical model which calculates the transmission of the piezoelectric actuator vibration to the liquid flowing in the reactor. Depending on the frequency at which the actuators are driven, a standing sound wave is excited in the channel (resonance mode). In this resonance mode, the acoustic pressure will strongly couple with the fluid, leading to a secondary flow structure with vortical motions, strongly enhancing species transport (acoustic streaming).

As a proof-of-principle, this reactor has been applied to the self-supported paired synthesis of dibenzyl (from benzyl bromide) and acetophenone (from 1-phenyl-ethanol). For this particular reaction, we used nickel as anode material and silver for the cathode. The experimental results prove, that when switching from silent to sonicated electro-synthesis, the throughput of the reactor is increased by an order of magnitude. Thus, ultrasound irradiation to excite acoustic streaming can be successfully applied for the intensification of continuous electrochemistry.

References

Keywords: microreactors, electrochemistry, ultrasound, process intensification
Exploring New Chemical Territory through Use of Flow

Timothy Noël

Eindhoven University of Technology, Department of Chemical Engineering & Chemistry, Micro Flow Chemistry & Synthetic Methodology, Eindhoven, The Netherlands
E-mail: t.noel@tu.nl

Until recently, many reactions have been exclusively performed in conventional batch LabWare. With the advent of microreactor technology, significant effort has been devoted to develop a wide variety of continuous-flow techniques to facilitate organic synthesis. Microreactor technology offers several advantages compared to traditional batch reactors, such as, enhanced heat- and mass-transfer, improved irradiation, safety of operation and the possibility to integrate several reaction steps and subsequent separations in a single streamlined process.[1]

Our group has taken a great interest in assisting chemists by developing automated and flow-based reaction technologies capable of reducing manual labor, increasing the reproducibility of the results and accelerating reaction discovery. In this presentation, we will give an overview of our synthetic methodology development, exemplified by photoredox catalysis,[2] cross-coupling[3] and electrochemistry[4] and how these synthetic methods were impacted by continuous-flow microreactor technology. Furthermore, we will discuss the developed technology and reaction models in detail.

References


Keywords: photochemistry; photoredox catalysis; electrochemistry; solar chemistry; flow chemistry
In-line Sampling and Analysis for Flow Continuous Chemical Manufacturing

Michael Organ

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In-process reaction monitoring with GCMS, LCMS, and NMR spectroscopy has been developed to accurately track reaction performance. This has facilitated the incorporation of feed-back loops between the reactor effluent stream and the front end of the reactor using in-house developed software for hands-free continuous reaction optimization and production monitoring.

Of course, samples must first be extracted from continuous processes in order to perform the above mentioned in-line analysis. This is often times thwarted by the presence of solids in the flowing stream, which can both block lines and valves and make analyses inaccurate. We have developed technology for the reliable handling of samples that contain solids from flow streams. This will be discussed in the lecture.
A Multiwavelength Photoreactor for Batch and Flow Chemistry – Development and Applications

Gellért Sipos1,2, Imre Károly Varga1, Kristóf Bodroghy1, László Dános,1 Tamás Zborovszky1

1 ThalesNano Inc., Budapest, Hungary
2 ComInnex Inc, Budapest, Hungary
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Recently, photoredox catalytic and other photochemical methodologies, together with technological advancements has enabled the invention of a vast number of powerful methodologies for bond construction.1

Having the right technology in hand is oftentimes crucial in order to achieve high yielding photochemical transformations.2 Our team developed a multifunctional photoreactor capable of performing batch and flow chemistry applying multiple wavelengths at a time. We present here the first applications of this instrument to a variety of photochemical transformations.

Although the Minisci reaction is a synthetically useful tool for the functionalization of heterocycles, it sometimes suffers from harsh conditions, low yields and selectivities.3 First, we investigated photochemical Minisci conditions in batch using the multifunctional photoreactor. Next, building on the batch results we devised a continuous microflow procedure. The in situ formed N-(acyloxy)phthalimide esters (NAP) in combination with transition metal based photoredox catalysts or organic dyes were employed for the alkylation of six- and five-membered heteroaromatic ring systems. The flow procedure allowed for the convenient integration of NAP intermediate formation and the subsequent coupling reaction.

References


Keywords: photochemistry, flow, Minisci reaction, photoredox
Introduction

A significant amount of new synthetic routes are discarded because they seem to fail or lead to poor results. Those discarded syntheses may have not necessarily failed at all but rather have been conducted at poor process conditions. Improving some of these conditions and enabling new, “forbidden” routes was successfully shown by changing from batch to flow chemistry [1]. However, continuous flow alone might not directly lead to optimal reaction conditions since mixing efficiency and mass transfer limitations are often not controlled or an ideal reactor behavior is assumed.

This work focuses on the design and manufacturing of customized milli- and micro reactors for flow chemistry at real and optimized process conditions. Optimization is possible through a workflow which combines interdisciplinary work ranging from optimizing reaction conditions, reactor design utilizing advantages of additive manufacturing, CFD simulation at prevailing process conditions, experimental performance characterization, as well as the final evaluation of the novel reactor in an industrial setting.

Customizing reactors is possible through a parameter depending CAD design, which is driven by a design tool linked to a 3D structure database. Structure database elements are evaluated experimentally through mixing-sensitive reactions, as well as in silico through automated CFD simulations that are connected to a database. The connection of peripheral equipment to the customized reactors is achieved by integrating connector and sensor port design already in the CAD designs.

Results

To give a detailed description of the workflow, the step-by-step approach is presented for two different design cases, which led to efficient 3D printed reactors (Figure 1 and 2) for continuous difluoromethylations using fluoroform [2] and aerobic oxidation of Grignard reactants [3]. In the latter case the reactor design was guided by real-time monitoring of the oxygen consumption rate using novel optical inline oxygen sensors [3] in a CSTR (continuous stirred tank reactor) cascade (Figure 2). The 3D printing of the reactors was done via Selective
Laser Melting (SLM) or lithography-based ceramic manufacturing (LCM). After printing and characterization, the final step was the performance comparison of the novel reactors to state-of-the-art equipment.

**Figure 1**: Stainless steel reactor for continuous difluoromethylations [2] (left). Rendered CAD image of an arbitrarily scalable reactor featuring split and recombine reaction sections [3] (right).

**Figure 2**: CAD image (left and middle) and 3D printed CSTR cascade closed with standard HPLC fittings [3].

This work is part of the CC Flow project (Center for Continuous Flow Synthesis and Processing, http://goflow.at/cc-flow).

**References**


**Keywords**: additive manufacturing, reactor design, inline sensor integration, 3D printing, selective laser melting (SLM)
Flow Reaction Calorimetry and Process Spectroscopy: Modern Tools for Efficient Reaction Screening and Integrated Process Control

Juergen Antes, Dusan Boskovic and Stefan Loebbecke

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Introduction

Monitoring and control of chemical processes in real-time is a key for increased efficiency, productivity and reproducibility. Particularly in-line analytical methods with high temporal and/or spatial resolution can provide most relevant information for optimization and safe scale-up of chemical reactions. Many chemical processes offer significant scope for improvement through detailed analysis of the physical-chemical processes on which they are based.

Here, we report on the development of spectroscopic and calorimetric process analytical tools for the real-time monitoring of chemical reactions in microfluidic processes.

Flow Reaction Calorimetry

Calorimetry is a universal analytical method for investigating thermal effects resulting from either exothermic or endothermic chemical reactions that allows gaining valuable thermodynamic and kinetic data for the successful design and intensification of chemical processes.

Over the past decade, we have been developing various continuously operated reaction calorimeters on the basis of flow reactors, which permit rapid screening of chemical reactions with regard to their thermo-kinetic parameters. At the heart of these calorimetric systems are miniaturized thermoelectric sensor arrays for the localized, quantitative measurement of heat flows and reaction enthalpies. The combination of flow chemistry and real-time heat flow measurements thus opens the way to a precise analysis of particularly fast chemical reactions. Moreover, targeted investigation and quantitative analysis of the energetic potential of critical process conditions (worst-case scenarios) can be conducted safely.

Process Spectroscopy

In-line spectroscopic tools and sensors are of ever-growing importance in the field of flow chemistry. Depending upon the scope we develop and apply versatile spectroscopic methods in a wide wavelength range (Infrared, Raman, UV/Vis/NIR) for deliberately monitoring chemical species during the course of a reaction.

For laboratory applications, vibrational spectroscopy is highly suitable as it provides detailed structural information on chemical transformations, which are particularly important at an early stage of reaction design and process development. Moreover, in the mid-IR region, new measurement techniques employing semiconductor lasers are emerging. So-called
Quantum Cascade Lasers (QCLs) offer high spectral brightness and fast spectral tuning in the kHz-range [1]. This allows overcoming certain restrictions that are usually associated with FTIR spectroscopy, i.e. difficult process integration and the need for particularly short path lengths.

Visible spectroscopy – although being less specific than other spectroscopic techniques – is a cost-effective method that is easy to adapt to flow chemistry processes and allows very fast and spatially resolved measurements. For example, we have modified a hyperspectral imager in order to allow simultaneous acquisition of Vis spectra at multiple discrete measuring points in a flow reactor. This type of spatially resolved spectroscopic monitoring of chemical reactions in combination with a closed loop control allows for early detection of decomposition products in any part of the reaction zone and immediate adjustment of process parameters. This analysis and control strategy contributes significantly to the overall process safety and additionally allows for more efficient reagent consumption.

References

[1] Ostendorf et al., Photonics 2016, 3(2), 28

Keywords: Flow calorimetry, in-line spectroscopy, process control, reaction optimization
Flow Synthesis of Cytotoxic Compounds

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Our team has invested considerable time and effort towards the synthesis of novel cytotoxic agents. Some targets have relied on phenotypic approaches to screening, while others have focused on the development and validation of novel cancer targets. Our interests lie in the more complex cancer targets, e.g. pancreatic cancer, glioblastoma and metastatic breast cancer.

This talk will examine how various flow chemistry technologies (flow synthesis, hydrogenation, photochemistry, etc) have enabled the synthesis of highly cytotoxic compounds targeting protein phosphatases,\(^1\) dynamin GTPase\(^2\) and most recently the arylhydrocarbon receptor.\(^3\)

References


Keywords: flow hydrogenation, flow photochemistry, cytotoxic compounds
Ultrafast Electrophilic Hydroxylamination under Safe and Scalable Continuous Flow Conditions

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This lecture illustrates our most recent efforts in designing integrated, modular and scalable continuous flow processes for the preparation of active pharmaceutical ingredients (APIs) and analogs. In particular, we will discuss the development of a general electrophilic hydroxylamination procedure. This work relies on highly reactive and toxic species that come with a unique reactivity profile. The process has a high atom economy; it relies on affordable and stable precursors for the preparation of high value-added molecules. Dozens of precursors and analogs of APIs, including WHO essentials and drugs on shortage, are prepared within minutes according to a fully concatenated process. The process features sequential modules with distinct unit operations including chemical transformations and multiple on-line extractions. The process is amenable to pilot scale, and features several layers of on-line analytical procedures to improve process safety and control.

Keywords: Continuous manufacturing / Active pharmaceuticals / Chemical library
Applications of Flow Photochemistry towards Industrial Scale Processing

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In recent years the popularization of synthetic photochemistry has brought with it a plethora of new methodologies, significantly enriching the chemist's synthetic toolbox. Alongside classical UV-mediated photochemical methodologies, modern visible light methods (including photoredox transformations) are now being routinely included in synthetic routes at a small scale. These often offer unique disconnections, unachievable by alternative means, therefore, an efficient scale up strategy must be capable of including such transformations. As these molecules progress through stages of development, the process chemistry and manufacturing communities must be prepared, in terms of both equipment and expertise.

Despite the inherent scalability implied by continuous flow processing, numerous obstacles are still present, including: reactor fouling, particularly when using UV irradiation; long reaction times, leading to low productivity; control of light flux over prolonged periods; and many more. With some extent of fundamental understanding around the reaction's kinetic regime and irradiation requirements, the most suitable reactor and conditions can be chosen or developed. Accordingly, these obstacles can be overcome, or at least minimized, towards a robust and productive process.

Figure 1. An example photochemical transformation performed in continuous flow, which has been scaled to >100 g, with a strategy identified for further scale up.

Herein, we present our experiences in developing a range of modern and classical photochemical transformations in continuous flow, in collaboration with industrial partners. These case studies will include: direct excitation and sensitized transformations, LED and arc lamp irradiation, tubing and plate-based reactors. The practical considerations, hurdles and solutions will be discussed, whilst maintaining a focus on application to processing on larger scales.

Keywords: photochemistry, photoredox catalysis, scale-up, LED technology
ROAR: Ushering in the Era of Data-driven Chemistry (Synthesis 4.0)

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The way synthesis is practised has changed substantially in the last decade: moving away from slow, labour-intensive manual methods, to highly automated, data-driven approaches. The use of high-throughput automated equipment is routinely used to execute a large number of reactions in parallel, for screening multiple reaction parameters, such as to optimise reactions quickly. Similarly, there is a wider use of analytical tools, enabling reactions to be carried out and monitored in a highly controlled and reproducible manner.

Going forwards, there is an increasing demand for chemists to collect high-quality large dataset, in order to extract reaction understanding and to validate Machine Learning algorithms.

The Centre for Rapid Online Analysis of Reactions – ROAR (http://www.imperial.ac.uk/rapid-online-analysis-of-reactions/) was set up in 2018 at the new Molecular Sciences and Research Hub at Imperial College London to provide access state-of-the-art automated equipment, aiming to transform the landscape of synthetic chemistry in the 21st Century. In this presentation, a number of exemplar projects will be presented, to demonstrate the value of adopting a data-driven approach to the development of synthetic chemistry.

![Figure 1: An overview of ROAR](image-url)

**Keywords:** Synthetic chemistry, reaction data
All You can do with Segmented Flow

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Flow chemistry is a rapidly developing technology that enables batch-to-continuous synthesis from lab scale to industrial production. Monophasic flow, including liquid flow through a fixed bed of solid (cartridge), is the dominating contacting motion since most of the chemistry is monophasic, or performed with a solid catalyst. However, segmented flow is largely used when two fluid phases – one phase being a liquid, the other being either a gas or a liquid – are used. Segmented flow could typically be observed in small tubes or capillaries found in many flow chemistry equipments. The very specific fluid motions of segmented flow lead to very efficient mixing and mass and heat transfer. Furthermore, more than two fluid phases could be contacted and solids could also be transported at quite high loadings (Fig. 1a & 1b). Such versatility opens the way to many applications in catalysis and material synthesis. During the lecture, examples concerning reaction-extraction, solid catalysts transport as slurry for hydrogenation reactions, combination of segmented flow with Open Cell Foams (OCF) as catalyst supports for the exothermic hydrogenation of terpenes or screening of reactions will be presented. Very exothermic and fast O₂ oxidations of organics are also performed with scale-up example to several kg. Last, the synthesis of metallic nanoparticles of Ru and RuCu with very interesting size and size distribution could also be performed in hydrogen-ionic liquids segmented flow. Finally, segmented flow could also be used as a compartmented reactor in which non-compatible reactions could be coupled to operate cascade catalysis (Figure 1e and 1f).

References


[5] The work on alternated segmented flow is performed by Miss Camille Méhault with a PhD grant from the H2020 FET-OPEN project ONE-FLOW EU proposal 737266.

**Keywords:** hydrogenation, oxydation, millifluidic, compartmentation
Pharmaceutical processes often involve a solid component as either a reagent, catalyst, or product. Processing of these solid components presents a challenging obstacle as it renders systems vulnerable to fouling and clogging. As a result, unit operations that require the handling of solid components are often performed in sufficiently large batch vessels that are less likely to plug. However, from a process intensification standpoint, it is desirable to miniaturize and develop other processing techniques that can improve heat and mass transfer while maintaining or improving product quality and uniformity.

Selection of the optimal small-scale reactor technology in these applications, however, is non-trivial and requires a thorough understanding of the reaction kinetics, flow patterns, and phases. A toolbox approach was developed by Plouffe et al.\(^1\) in order to facilitate reactor selection based on these parameters, but remains underdeveloped for micro and milli scale reactors where solids are present due to their inevitable amplification of the difficulties in solid handling. Furthermore, a review by Roberge \textit{et al.} of 86 reactions carried out at Lonza concluded that 50% would be improved by moving into continuous microreactor processing, but 63% of those candidate reactions cannot be performed due to the presence of solids\(^2\). A miniaturized, intensified processing unit that can continuously handle solids without clogging or losing performance over an entire production campaign would be highly valuable to the pharmaceutical and fine chemical industries.

The solid handling ability and flow patterns of a baffle-less oscillatory flow coil reactor are investigated and characterized. Previous works in oscillatory flow have been generally conducted in straight channel baffled reactors at lower oscillatory Reynolds numbers than the present work. Solid handling capabilities of the reactor are examined through two reactions, namely a precipitation reaction and a phase transfer catalysis reaction with potential gas formation.

References


Keywords: Continuous Solid Handling, Oscillatory Flow Coil Reactor, Plugging
Modeling and Time Scale Analysis of Processes at the Micro Scale

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Introduction

The intensification and optimization of existing chemical and biochemical processes with better selectivity, highly efficient heat and mass transport, products quality, process safety, as well as the development of new and environmentally friendly technologies are feasible with the microreactor technology, where the modeling-based design plays an essential role [1].

Time-Scale Analysis and Characteristics Times are suggested as a novel and useful tool in the analysis of the performance of microscale-based reactors, unit operations, and plant flow sheet diagrams envisioned as microscale-based chemical processes. Transport phenomena, reaction kinetics, and phase contacting in microstructured architecture can be easily represented by unique time constants, \( \tau_i [s] \), which enable observing/understanding these processes through the lens of Characteristic Times (Figure 1). The origin of Characteristic Times is in detailed mathematical models of microscale-based reaction processes and operations. The user-defined scaling parameters contribute to the flexibility of TSA implementation.

In this work, we demonstrate the feasibility and usefulness of this novel tool in the field of chemical reaction engineering – exemplified by the use of TSA in the preliminary analysis of solid-catalyzed chemical reaction processes in microscale-based reactor. This novel technical approach can easily take place in the toolbox of practicing chemical reaction engineers [2]. Furthermore, the microscale process development is presented in combination with modeling-based optimization. Theoretical description of transport phenomena and the kinetics at the micro scale is discussed and illustrated on the cases of a lattice Boltzmann simulations for flow distribution in the packed bed microreactor and the biocatalytic enzyme surface reaction [3]. The multiscale modeling concept is demonstrated on the case of enzyme-substrate reaction in magnetic nanoparticle filled flow microreactor.
Figure 1.: Potential areas of implementation of the Time Scale Analysis and Characteristic Times.

References


Keywords: Microreactor Technology, Modeling, Time Scale Analysis, Multiscale Modeling
Application of Continuous-flow Catalytic Hydrogenation in Formation of Value-added Products

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Introduction

Continuous-flow processes offer significant advantages over batch reactions in terms of safety, efficiency, purification, durability, waste emission, reproducibility, automation, energy and space consumption [1,2]. Due to the fact that catalytic hydrogenation is one of the most widely applied methods in chemical industry and environmental protection, recent studies focused on development of continuous-flow systems for catalytic hydrogenation with heterogeneous catalysts [1-3]. Hydrogenation is usually carried out using noble metals such as Pd Pt, Rh, Ru Ir [3] as catalysts. Although they are very active in the hydrogenation process, operating at low temperatures and H₂ pressures, their high cost intensified the research aimed at finding alternative catalysts containing lower amounts or deprived of noble metals.

Therefore, our research strategy concentrates on application of continuous flow in catalytic reactions with readily available 3d transition metals (e.g. Ni), of importance in pharma and fine chemicals technology such as:

- chemoselective hydrogenations of α,β-unsaturated aldehydes and ketones (e.g. cinnamaldehyde, citral, prenal, 6-methyl-5-hepten-2-on) towards vitamins and fragrances precursors,
- catalytic nitrocyclohexane hydrogenation towards value added products (e.g. cyclohexanone oxime, cyclohexylamine).

Experimental

Continuous flow system – ThalesNano™ HCube Pro – was used both for heterogeneous catalyst modification by surface organometallic chemistry approach and for catalytic hydrogenation processes. Adequate amount of powdered catalyst (50-150 mg) was placed in a stainless steel cartridge (CatCart®70, 4 mm i.d.), which was subsequently connected to the apparatus. Hydrogen was generated in situ via electrolysis of water. All of the catalysts were thoroughly investigated using different physicochemical methods, such as: TPR, TPHD, BET, CO chemisorption, PXRD, STEM and XPS at different stages of their biography.

Results and discussion

Nickel particle size modification was investigated in the accretion/reaction protocol in flow to evaluate the structure-performance relationship in the chemoselective citral hydrogenation over Ni-based catalysts. Implementation of this methodology allowed determination of the optimal nickel nanoparticle size (9 nm) that ensures efficient citral hydrogenation towards the desired product –citronellal [1].
Similarly, synthesis of bimetallic NiSn catalysts was achieved by means of post-synthetic modification of the parent catalyst via surface organometallic chemistry approach and was performed in the same flow microreactor, which was used for the catalytic studies, providing a methodology for online modification of parent catalysts. It was shown that addition of Sn to Ni nanoparticles grafted on resin decreases the binding affinity of the unsaturated substrate towards metal nanoparticles and leads to a switch in selectivity so that C=O hydrogenation product interacting with the catalyst is more thermodynamically stable as compared to the C=C hydrogenation product Fig. 1.[4].

**Figure 1.** Selectivity toward C=C and C=O hydrogenation of 6-methyl-5-hepten-2-one for NiSn0.12TSNH2. Reaction conditions: T= 100°C, pressure = 40 bar

**Conclusions**

Application of a flow system is an effective approach to efficient hydrogenation towards value-added products of importance in various industry sectors.

**References**


**Keywords:** continuous flow hydrogenation, catalysis
Poster presentations
Methylation with Chloromethane in a Microreactor

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Chloromethane (methyl chloride, CH₃Cl) is a methylating agent widely used in industry. However, investigations at laboratory scale are complicated by the need for special equipment and safety measures as chloromethane is a flammable gas suspected of causing cancer.

Microreaction technology offers several advantages for the investigation and intensification of processes using chloromethane such as a low hold-up and easy accessibility of high pressures in addition to excellent mass and heat transfer characteristics.

In this work, a microreactor plant has been designed to study the methylation of amines with chloromethane in a biphasic liquid-liquid system under pressure in safe conditions. A capillary microreactor setup has been chosen that allows for experimenting under nearly isothermal conditions with negligible mass transfer limitations in order to obtain reliable and reproducible kinetic data. This data is used to establish a detailed kinetic model with mechanistically rationalized rate equations that can be used for process optimization and scale-up purposes. Here, the methylation reaction of morpholine is investigated, which affords a mixture of Nmethylmorpholine and a quaternary morpholinium salt.

Figure 1: Setup of the lab-scale microreactor plant (1: lab automation system; 2: CH₃Cl gas cylinder; 3: syringe pumps; 4: thermostat with immersed microreactor; 5: autosampler; 6: scrubber).

Keywords: kinetics, methylation, microreactor
Organofluorine compounds are interesting molecules with broad applications in medicinal chemistry, material chemistry and agrochemistry.1,2 The development of new synthetic strategies to access new molecules with fluorinated moieties still remains a challenge for organic chemists and a “hot topic” in modern synthesis. The importance of organofluorine chemistry is showcased by the presence of fluorine in nearly 20% of all pharmaceuticals and 35% of agrochemicals on the market.3 It is therefore noteworthy to develop effective synthetic strategies, either for the incorporation of fluorine atoms into organic scaffolds or for the preparation of fluorinated building blocks. In this communication, we report our contribute in the development of strategies for direct fluoroalkylation.4,5 The potential of flow microreactor technology in fluoroalkylation chemistry will be also reported.

References


Keywords: fluoroalkylation, flash chemistry, flow microreactors
Transaminases are pyridoxal-5’-phosphate dependent enzymes which can catalyze kinetic resolution of racemic amines or asymmetric synthesis of enantiopure amines starting from prochiral ketones. \(^\text{[1]}\) Asymmetric synthesis would be more preferred, although, it usually suffers from disfavored reaction equilibrium and requires expensive amino donors. Kinetic resolution applies the thermodynamically more favored reaction but a selective transaminase result in only one enantiomer (maximal 50% yield) of the racemic amine after converting the other into the corresponding ketone. \(^\text{[2]}\) If the ketone formed could also be converted to the desired enantiomer, complete conversion could be achieved. Principally, another transaminase of opposite enantiomer selectivity is capable of such transformation.

Consequently, we set up a cascade reaction system including two immobilized transaminases of opposite enantiomer preference. To improve the sustainabilita of the process, the cascade system applying miniaturized packed bed reactor system operated in continuous-flow is designed (Figure 1).

**Figure 1:** Continuous-flow deracemization of amines with two immobilized stereocomplementary transaminases

**References**


**Keywords:** continuous-flow, biotransformations, deracemization, transaminase
The contemporary, pressing need for sustainable chemical reactions has raised the demand for economic friendly processes that expand the conventional synthetic toolbox and proceed with the generation of minimal waste. In many cases, the use of dedicated flow equipment has proven its value and can bring doubtless advantage for chemists in the laboratory. [1] The hazardous or sensitive nature of some chemicals makes handling at conventional lab or industrial scale difficult. [2] In the original industrial scaled method of the antifungal agent terbinafine (5) after an organometallic step by butyllithium, acrolein is used to get the vinyl alcohol intermediate (3). [3] Thus acrolein is toxic, irritative and flammable, we envisioned a continuous synthetic route without this hazardous reagent, where organometallics can be used with relatively low risk owing to flow technology. After the metatation of but-1-yn (2) ethyl formate was added to form the corresponding aldehyde and in the next Grignard reaction the vinyl alcohol structure (3) was formed successfully.

This work was performed in the frame of FIEK_16-1-2016-0007 project, implemented with the support provided from the National Research, Development and Innovation Fund of Hungary, financed under the FIEK_16 funding scheme.

References

Keywords: terbinafine, continuous flow, organometallic reaction, flash chemistry
In recent years, a lot of effort has been put into the development and implementation of continuous flow processes. Owing to their diverse benefits including improved energy efficiency and increased safety [1], the Federal Drug Administration (FDA) aims for the application of continuous flow technology in pharmaceutical manufacturing [2]. In this context, the goal of the ONE-FLOW project [3] is the development of multistep catalytic cascades for the synthesis of top-list drugs in a continuous fashion. Being part of this project, one of our objectives is the continuous synthesis of valsartan, active pharmaceutical ingredient of Entresto® (Novartis) for the treatment of hypertension and chronic heart failure [4]. Our approach for the synthesis of a late-stage precursor of valsartan involves three steps including \( N \)-acylation, Suzuki-Miyaura cross-coupling and methyl ester hydrolysis. The key step of the reaction cascade, the formation of the biphenyl core via Suzuki coupling, is facilitated by heterogeneous Pd-Ce-Sn oxides [5]. Using a combination of coil reactors and a packed-bed reactor, we were able to synthesize the target compound in continuous flow with up to 96% overall yield (see Figure 1).

**Figure 1:** Realized multistep synthesis of a valsartan precursor in continuous flow

The authors kindly acknowledge the funding by the H2020-FETOPEN-2016-2017 programme of European commission (Grant agreement number: 737266-ONE FLOW).
References


**Keywords:** continuous flow, multistep synthesis, One-Flow, valsartan
A Multistep Flow Synthesis of Tricyclic Benzimidazole Derivatives

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Nitrogen containing heterocycles bearing benzimidazole moieties are in the focus of drug discovery interest due to their pharmacological applications as antitumor,[1] anti-inflammatory,[2] analgesic [3] and antibacterial [3,4] agents. However, the known synthetic methods suffer from minor drawbacks such as use of corrosive and toxic catalysts, high temperatures, low yields and comparatively long reaction times. In order to find an efficient and environmentally benign method we decided to develop a multistep flow synthesis of benzimidazoles (3) and pyrrolobenzimidazoles (4) involving N-acylation and intramolecular reductive cyclization starting from substituted o-nitroaniline (1) and dicarboxylic acid anhydrides (2).

![Figure 1: Flow synthesis of benzimidazoles 3 and 4](image)

This work was performed in the frame of FIEK_16-1-2016-0007 project, implemented with the support provided from the National Research, Development and Innovation Fund of Hungary, financed under the FIEK_16 funding scheme.

References


Keywords: benzimidazole lactam, heterocycles, continuous flow, domino synthesis
The progressive depletion of fossil resources and a global environmental awareness stimulates research toward a transition for more sustainable resources. Glycerol, which is nowadays obtained as a by-product of the biodiesel production, presents a significant industrial potential and can be upgraded in a large variety of value-added building blocks.[1]

We present herein a robust multi-module continuous flow procedure for the valorization of glycerol towards active pharmaceutical ingredients (APIs) through the intermediate formation of epichlorohydrin. The first module is dedicated to the valorization of glycerol into oxiranes (glycidol and epichlorohydrin) by a hydrochlorination/dechlorination sequence. The concatenable system relies on economically and environmentally favorable conditions involving an organocatalyst and aqueous solutions of HCl and NaOH. Pimelic acid was highlighted for its exceptional catalytic activity for the hydrochlorination step (>99% conv., 81% select. for intermediate chlorohydrins). The dechlorination step was directly telescoped with the hydrochlorination affording a ca. 3:2 separable mixture of epichlorohydrin (in MTBE, with optional concentrator) and glycidol (in water) in 74% cumulated yield from biobased glycerol. Next, biobased epichlorohydrin is further utilized for the continuous flow preparation of β-amino alcohol APIs including propranolol (hypertension, WHO essential), naftopidil (prostatic hyperplasia) and alprenolol (angina pectoris) within a concatenable Williamson/aminolysis sequence using a FDA class 3 solvent (DMSO). This work provides the first example of direct upgrading of biobased glycerol into high value-added pharmaceuticals under continuous flow conditions.[2]

References

Keywords: Valorization, Biomass, API, Continuous Flow
**P-08**

**Control of Random Copolymerization by Sequential Monomer Addition Using Flow Microreactors**

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Random copolymers have attracted a great deal of attentions because they are expected to be used for various functional materials. However, when monomers having different reactivities are used for random polymerizations, it is difficult to arrange the monomers at random because highly reactive monomers are preferentially converted to polymer. The use of an integrated flow microreactor system were examined to solve the problem. The precise residence time control by flow microreactor allows the sequential monomer addition during polymerization. For example, the anionic polymerization of tert-butyl methacrylate (tBuMA) and di (ethylene glycol) methyl ether methacrylate (MEO₂MA) were carried out using a flow microreactor system composed of four T-shaped micromixers (M₁, M₂, M₃ and M₄) and four microtube reactors (R₁, R₂, R₃ and R₄). The initial concentration of MEO₂MA, highly reactive monomer, was set low and then added sequentially. Therefore, the synthesis of random copolymer could be successfully accomplished.

![Flow microreactor system for anionic copolymerization by sequential monomer addition](image)

**Figure 1:** Flow microreactor system for anionic copolymerization by sequential monomer addition (M₁, M₂, M₃, M₄: T-shaped micromixer, R₁, R₂, R₃, R₄: micro tube reactor).

**References**


**Keywords:** Flow Microreactor, Anionic Polymerization, Random Copolymerization
P-09
Hydrothermal Synthesis of CdSe Quantum Dots Using Continuous Flow Chemistry

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Currently, most process synthesizing CdSe QDs use organic solvents which permit reaction at high temperature [1]. In this poster we describe our most recent advances to synthesize CdSe QDs in water using advanced continuous flow technologies. It is, therefore, necessary to produce water soluble selenide precursor, compatible with flow chemistry. In this purpose, we investigated new reducing agents allowing the formation of selenide precursor, from oxidized or neutral forms of selenium. In a second time, the selenide so-formed was engaged in a reaction with Cd$^{2+}$ to form CdSe QDs. The influence of parameters such as temperature, pressure, residence time and ligands under the size and the fluorescence of the QDs were estimated [2].

References

Keywords: Quantum Dots (QDs), CdSe, continuous-flow chemistry
An Expedient Flow Chemistry Approach to Substituted 1,4-Dimethylcarbazoles

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The carbazole scaffold is an integral part of a number of compounds of interest in medicinal chemistry, including ellipticine (1) and wiskostatin (2). This work explores the synthesis of substituted carbazole scaffolds, starting from substituted indoles and 2,5-hexanodione, utilising montmorillonite as a catalyst under flow conditions.

The alkaloid natural product ellipticine (1) (5,11-dimethyl-6H-pyrido[4,3-b]carbazole) was originally isolated from Ochrosia elliptica Labill (Apocynaceae)¹ and has displayed anticancer properties against osteolytic breast cancer metastases, kidney sarcoma, brain tumors and myeloblastic leukemia.[2]

Wiskostatin, and its inhibition of the protein N-WASP has been identified in reducing the motility of lung cancer cells.[3]

The expedient synthesis of the carbazole scaffold allows rapid access to a variety of substituted carbazoles for further exploration of the anticancer properties of these compounds.[4]

References

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Keywords: carbazole, montmorillonite, ellipticine, wiskostatin
Continuous Flow Synthesis of α-Aminophosphonates

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Although flow chemistry may be considered as one of the most innovative directions of synthetic chemistry, only a few examples can be found in the field of organophosphorus transformations [1]. α-Aminophosphonates are the phosphorus-analogues of α-amino acids [2]. Due to this similarity, they are of potential biological activity. These important organophosphorus derivatives were prepared by the three-component Kabachnik–Fields reaction of primary amines, benzaldehyde derivatives and dialkyl phosphites in a CEM® microwave (MW) reactor equipped with a CEM® flow cell (Figure 1) [3]. A few target compounds were also synthesized by the MW-assisted continuous flow Pudovik reaction. Beside the optimization of the reactions, we have also investigated the hydrodynamic properties of the flow cell to determine the upper and lower flow rate (or residence time) limitations of the continuous flow MW system applied.

Acknowledgements

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References


Keywords: α-aminophosphonates, continuous flow microwave system, Kabachnik–Fields reaction, Pudovik reaction
Novative Strategy towards Oxazine Free Amines from a Novel Class of Photocleavable Acyl Nitroso Featuring Key Photochemical Steps under Continuous Flow Conditions

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Throughout this research program the preparation of (bicyclo)-3,6-dihydro-1,2-oxazines bearing a free amine was studied. The developed synthetic strategy relies on the unprecedented nitroso hetero Diels-Alder (nHDA) reaction between (non)cyclic dienes and a photolabile acyl nitroso species which acts as a highly reactive dienophile. The developed strategy is composed of 4 chemical steps. In the first step, the preparation of a chloroformate intermediate is conducted by reacting the alcohol derivative of the nitropiperonal moiety (which is a known photolabile protecting group) with a phosgene analogous. The second step relies on the preparation of the key hydroxycarbamate intermediate by reacting the chloroformate species with hydroxylamine hydrochloride. The third step is the in situ oxidation reaction of the key hydroxycarbamate intermediate into the desired acyl nitroso species which will act as a highly reactive dienophile with (non)-cyclic dienes. A photochemical alternative under continuous flow operation is also envisioned. Upon reaction, the cycloadduct can be photocleaved under microfluidic conditions in the last step to yield the desired oxazine moiety bearing a free amine (see Figure 1).

Figure 1: Synthetic strategy towards (bicyclo)-3,6-dihydro-1,2-oxazines bearing a free amine featuring key photochemical steps under microfluidic conditions

The designed strategy proved to be robust and efficient upon preparation of a library of cycloadducts with various non-cyclic dienes such as 2,3-dimethyl-1,3-butadiene or cyclic dienes of varying ring sizes ranging from cyclopentadiene to cyclooctadiene. Non-symmetrical dienes were also investigated such as the terpinene derivatives. Using our designed acyl nitroso species, we observed a significant regioselectivity in the case of non-symmetrical dienes. Finally, successful photocleavage of the nitropiperonal moiety was
conducted upon irradiation of the cycloadduct under microfluidic conditions yielding the desired oxazine bearing a free amine.

**Keywords:** Acyl nitroso, Hydroxycarbamate, Hetero Diels-Alder, Continuous flow
Artemisinin is a secondary metabolite of the plant *Artemisia annua* and an important precursor to several active pharmaceutical ingredients (API) which are used for treating malaria. Artemisinin is still mainly produced by extraction of the plant resulting in high prices for the API and shortages of supply. One approach to make artemisinin-based medications more widely available is to synthesise additional artemisinin obtained from extraction by utilizing dihydroartemisinic acid (DHAA) - a precursor to artemisinin. Co-extracted DHAA can be converted to artemisinin in a reaction sequence consisting of an initial photosensitized step and a consecutive acid-catalyzed reaction sequence. The partial synthesis needs to be performed in a mini-channel reactor to ensure high mass transfer rates between oxygen and the liquid phase and strong illumination of the whole reactant solution [1].

We demonstrated recently that the cost-intensive photosensitizers previously used in the semi-synthesis can be substituted by utilizing chlorophyll – a second byproduct of the extraction [2]. In order to find also an alternative to the currently applied trifluoroacetic acid for the second reaction step, we tested a wide range of heterogenous acids regarding their applicability for the semi-synthesis of artemisinin. The best performing candidates were identified and applied in continuous operation in packed beds. Based on these results different reactor configurations were tested to optimize residence time, phase distribution and mass transfer between the phases.

**Figure 1:** Reaction Scheme of the partial synthesis of artemisinin
References


Keywords: Solid acid catalysis, multiphase reactor, natural product synthesis
FEP Microfluidic Reactor for Photochemical Reactions

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Fluoropolymers are a material of choice for many types of synthesis due to their chemical compatibility and low surface energy. Still, fluoropolymer microreactors for photochemistry-built with a transparent fluoropolymer, i.e. fluorinated ethylene propylene (FEP)-have until now been only constructed with sections of tubing.

Here, we demonstrate a ‘click’ system, where the two plates of FEP are joined together mechanically using a tenon and a mortise. The concept was presented by us previously for preparation of PTFE microreactor[1]. Here, we use the same strategy to FEP plates and test the use of the chips in photochemistry. The solutions that we describe offer tight microreactor chips, preventing any leakage both of the liquid reagents and of UV light outside the reactor. Our microreactor is compact (consists of equivalent of 75 cm of FEP tube, yet the whole chip has 32 cm²), easy to disassemble and clean. The use of CNC micromachining allows to design any microfluidic geometry, which makes it a very versatile system.

We provide a proof-of-concept verification of the use of this microreactor in two organic syntheses involving UV radiation: bromination of indanone with bromosuccinimide and thiol-ene reaction. This demonstrates that our microreactor made of FEP can be used effectively in organic laboratories performing photochemical reactions[2].

References

Keywords: FEP, microreactor, photochemistry, organic synthesis
Development of Segmented Flow Compartmentalization for Cascade Reaction in Continuous Flow

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Combining several reactions in one reactor can provide major benefits in terms of time, costs and efficiency. The ONE-FLOW project [1] aims to implement cascade reaction in continuous flow processes by using compartmentalized flow reactor system. The targeted cascade reaction for a ONE-FLOW process must follow certain criteria in order to gain advantages compared to a conventional separated process. For example, the targeted cascade reaction can have an unstable intermediate that would be directly consumed by the second reaction.

A promising approach for reactor compartmentalization at millimetric scale is the multiphasic segmented flow. A new type of segmented flow called the alternated segmented flow has been developed at the millimetric scale to perform coupled reactions in a same reactor. The idea is to generate two miscible yet chemically incompatible phases separated by a non-miscible inert layer (see Figure 1 a).

The difficulty in the compartmentalization technique is to avoid the coalescence of the miscible droplets for a relatively long resident time which requires studies on the hydrodynamic behaviour (see Figure 1 b and c).

Our objective is to use this compartmentalization technique to implement coupled reactions with one reaction in each droplet. In particular we focus on the chemoenzymatic cascade reaction to form 1-phenylethanol from styrene by coupling the Wacker oxidation of styrene and the enzymatic reduction of acetophenone. Both reaction media are miscible but incompatible due to the enzyme deactivation by the Wacker catalyst hence the need to use the alternated segmented flow.

Figure 1: a) Coupled reactions with an intermediate B that have to be directly extracted to avoid the formation of side products, b) Alternated L1/L2 segmented flow, c) Alternated L1/L2/G segmented flow

Our objective is to use this compartmentalization technique to implement coupled reactions with one reaction in each droplet. In particular we focus on the chemoenzymatic cascade reaction to form 1-phenylethanol from styrene by coupling the Wacker oxidation of styrene and the enzymatic reduction of acetophenone. Both reaction media are miscible but incompatible due to the enzyme deactivation by the Wacker catalyst hence the need to use the alternated segmented flow.

References


Keywords: cascade reaction, millifluidic, compartmentalization, segmented flow
On the Regioselectivity of the Gould-Jacobs Reaction: Gas-Phase vs. Solution-Phase Thermolysis

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The Gould-Jacobs reaction is a well known thermal cyclization for the construction of important heterocyclic compounds, such as pyrido pyrimidinones 3 and naphthyridinones 2. As reported by Lappin in 1948,[1] conventional heating of precursor 1 in solution leads to the thermodynamic product 2. Flash vacuum pyrolysis (FVP) is used for gaseous reactions at high temperatures (up to 800 °C) at high vacuum (10⁻³ mbar). Under these conditions very short reaction times (~1 ms) can be achieved, which could enable the generation of the kinetic product 3.

Herein we present the in-depth study of the regioselectivity of this cyclization reaction on compound 1 using different thermal activation methods in the gaseous or liquid phase. Computational studies for investigations on the regioselectivity will be discussed.

**Figure 1:** Regioselectivity of the Gould-Jacobs reaction

**References**


**Keywords:** Gould-Jacobs reaction, flash vacuum pyrolysis (FVP), regioselectivity, flow chemistry
Blue-light Enhanced Synthesis of Functionalized Biphenyls by Using a Capillary Photoreactor

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Functionalized biphenyls containing fluorine are important building blocks for active pharmaceutical ingredients.[¹] Biphenyls can be generally prepared by direct C-H arylation of the favored aromatic compounds with commercially available anilines. For this purpose necessary free radicals are obtained from diazo anhydrides, which are formed in situ by the aniline and an alkyl nitrite.[²]

Now, a synthesis route for CF₃-substituted biphenyls is elaborated. CF₃-biphenyls are produced by direct photochemical coupling of CF₃-aniline with benzene as benchmark. In batch mode, formation of desired free radicals is increased by irradiation with blue light. As a result, fragmentation of diazo anhydride is more selective and corresponding biphenyls are obtained in 75% higher yield. Adding titanium dioxide brings an additional beneficial photocatalytic effect of increasing yield by 40% extra. It is known that TiO₂-azoether intermediates show absorption of blue light and subsequent single electron transfer causes formation of the radicals.[³]

This synthesis route is furthermore transferred into a continuous-flow photochemistry approach by introducing a catalyst suspension into a gas-liquid slug flow.[⁴,⁵] The resulting three-phase mixture is then irradiated in a capillary photo reactor. To avoid settlement of the heterogeneous catalyst at the capillary walls, usage of a co-solvent is necessary to maintain slug flow. Triglyme as co-solvent provides the advantage that the formation of side-products such as 3,3’-(CF₃)₂-biphenyl is suppressed.

References

Keywords: photocatalysis, continuous flow, C-H arylation
Photochemical syntheses are typically influenced by a variety of different reaction parameters like the equivalents of substrates and additives, the nature of the solvent, or the concentrations. While these parameters are routinely screened during reaction development, systematic studies on the impact of the irradiation wavelength are mostly lacking. Here, we employ 16 LED arrays with different emission bands (350–700 nm) and photon-matched irradiation intensities together with a continuous-flow photoreactor. The perfluoroalkylation of 2-methylindole with eosin Y as photoredox catalyst was used as test reaction. Three different reaction channels could be gated wavelength-selectively which, in turn, were directly translated into three independent synthetic routes towards perfluoroalkylated indoles – photoredox-catalyzed, catalyst-free, as well as catalyst- and additive-free. Our results highlight the need for discrete light input to trigger discrete photochemical processes.

**Keywords:** photochemistry, flow chemistry, C–H activation
Light-Promoted Iron-Catalyzed Kumada CrossCouplings in Flow

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Metal-catalyzed cross-couplings are a most prominent class of C-C bond-forming reactions.[1] One of the oldest and most important is the coupling of aryl halides with Grignard reagents (Kumada coupling). Although mostly performed with Pd and Ni catalysts, more benign and sustainable Fe species also proved effective in promoting these reactions.[2] Moreover, aryl chlorides can be generally more efficiently utilized with Fe catalysis than with Pd and Ni, making this methodology attractive for synthetic applications.[2] Despite advancements in the field of Fe-catalyzed Kumada couplings, still many limitations exist, e.g. for electron-neutral and electron-rich aryl chlorides.[2,3] We recently discovered that Fe-catalyzed cross-couplings between aryl chlorides and alkyl Grignard reagents can be considerably accelerated under irradiation with blue light, allowing fast, room temperature coupling to occur for a number of challenging substrates, when performed under flow conditions.[4] These results will be presented here.

Electron-neutral and electron-rich aryl chlorides

Unprotected NH groups

References


Keywords: cross-couplings, flow photochemistry, iron catalysis
P-20
Synthesis of Phenacenes and Helicenes Using a Photochemical Flow Reactor

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Phenacenes and helicenes as a group of polyaromatic hydrocarbons (PAHs) have attracted a considerable attention due to their unique electronic and optical properties. Owing to their conjugated π-electron system, both of these groups are suitable for use in optoelectronics (OLED, OFET)\(^1\)-\(^3\). For utilization in these applications, sufficient solubility in common organic solvents is desired. In case of phenacenes, which are generally poorly soluble, substantial increase in solubility is achieved by suitable substitution or incorporation of nitrogen atom to their structure. Therefore, new compounds such as 1,2,3,4-tetrafluoro[5]phenacene, 1,2,3,4-tetrafluoro[6]helicene, 2,9-diaza[5]phenacene, 14-chloro-13-aza[5]phenacene, and 2,15diaza[6]helicene were prepared (Fig. 1).

![Figure 1: Phenacenes and helicenes](image)

The goal of this effort was to develop a multigram scale photochemical synthesis of phenacenes and helicenes from their stilbene precursors by photocyclization reaction. In the quest of our investigation, we have assembled a fully functional flow photoreactor, which is crucial for future research of phenacenes and helicenes.

References


Keywords: photocyclization, phenacene, helicene

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The recent emergence of self-optimizing flow reactors as powerful automated devices to assist chemists involved in the optimization of chemical reactions will profoundly impact organic synthesis in a near future. This groundbreaking technology associates flow reactors with process control instrumentation, in-line/on-line analysis techniques and optimization algorithms in a single autonomous device working without human intervention after initialization.

In this frame, based on our experience in flow chemistry,[1-3] we developed an autonomous self-optimizing flow reactor as a flexible platform enabling an adaptation of the experimental setup to the specificities of the chemical transformations to be optimized. The reaction monitoring uses either on-line high pressure liquid chromatography (HPLC) or in-line benchtop nuclear magnetic resonance (NMR) spectroscopy.[4] The custom-made optimization algorithm derived from the Nelder-Mead and golden section search methods performs constrained optimizations of black-box functions in a multi-dimensional search domain. This autonomous self-optimizing system allowed fast and efficient optimizations of various chemical reactions including metal-catalyzed transformations and even multi-step sequences.[5,6,7]

References


Keywords: Flow Chemistry, Real-time analysis, Algorithm, Autonomous
P-22

Rapid, Automated Identification of Reaction Models and Kinetic Parameters

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Introduction

A major bottleneck in transitioning from chemistry research to process development is a lack of quantitative chemical synthesis information. Important aspects of this information include the development of reaction kinetics - both the reaction model and kinetic parameters. If readily available, this information would allow for the application of classic reaction engineering principles to shorten process development time and lower costs.[¹]

During the chemical development lifecycle of fine chemicals and pharmaceuticals, experimental data from batch and semi-batch reactors tend to be used to estimate the unknown kinetic parameters of a proposed reaction model. This approach is still seen as a resource intensive and specialized activity.[²] We report the efficient use of transient flow data to generate isothermal reaction profiles, in conjunction with a Mixed-Integer Linear Programming (MILP) based approach to computationally determine both the reaction model and fundamental kinetic parameters of a chemical process with minimum cost.[³] The outline of this approach is described in Figure 1.

![Figure 1](image-url)

**Figure 1.** The computational approach used in these kinetic studies. Every possible reaction model, based on mass balance, is identified and quantitatively ranked based on the simplicity of the model and how accurately it fits the experimental data.
This work combines the ability to manipulate pump flow rates using automated flow ramps with integrated online HPLC analysis at the reactor outlet. Quantitative analysis of the relative changes in concentrations of all reactants, intermediates and products over time is then processed. All plausible kinetic schemata are assembled based on mass-balanced combinations of participating species, and minimisation algorithms are applied to determine all unknown reaction parameters using ordinary differential equation (ODE) solvers (Figure 2). Kinetic schemata are then ranked by a factor relating to the goodness-of-fit to the experimental data and the simplicity of the reaction model, thereby selecting the most accurate representation of the system.

![Figure 2. Transient flow data for the reaction of phenol and acetyl chloride producing phenyl acetate, where: x = phenol, y = phenyl acetate, — = phenol (ODE), — = phenyl acetate (ODE). The combination of MILP and minimisation algorithms identify the kinetic model as the ODE solver converges on the data, providing accurate and rapid kinetic parameter estimation.](image)

This work enables the rapid, automated identification of the reaction model and kinetic parameters for a reaction system by performing just one flow ramp experiment.

**References**


**Keywords:** Kinetics, Model Determination, Transient Flow, Optimisation, Minimisation Algorithms
Novel Building Blocks for DNA-encoded Libraries Using Open Collaboration Model and the Application of Flow and Photo Chemistry

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Pharmaceutical research is often carried out in silos as companies seek to protect the IP around their unique molecules. More recently the concept of the "pre-competitive space", which means activities or results that are either not directly contributing to the generation of a patent or are still far from the patentable item has given pharmaceutical companies areas of research where they can freely collaborate. The practise is well established in non-core activities like software development but has been less applied directly to early stage drug design. In the field of DNA encoded library synthesis there is acknowledged shortage of appropriate and novel building blocks. We show how an open innovation collaboration project involving 10 companies in total has led to the design and synthesis of over 300 new building blocks using our unique photochemical approach in flow as you can see on Figure 1.

Keywords: DNA Encoded Library, Open Collaboration, Photochemistry
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