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Science Agency

Australian Flow Chemistry Symposium

#AFCS19

2–3 December 2019 | Melbourne, Australia

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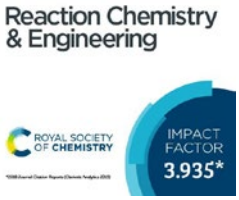


Welcome

CSIRO Manufacturing welcomes you to Australia's first Flow Chemistry Symposium.

This symposium brings together a growing Australian flow chemistry community and provides a dedicated platform where flow chemistry professionals from industry and academia can meet.

Over the next two days you will network with chemists, chemical engineers, material scientists and others active in the fields of flow chemistry and microreactor technology.

Our goal is to strongly focus on industrial applications for the chemical industry and demonstrate how continuous flow and microreactor technology can improve process efficiency and make chemical manufacturing safer, more compact, less wasteful and more economic.

Delegate Information

Locations

Sessions: State 1 and 2

Exhibition, posters and breaks: State 3

Conference dinner on Monday: Lake rooms.

Registration Inclusions

Delegates will receive the following goods and services as part of their registration:

- Access to conference sessions
- Conference program booklet
- Morning tea, lunch and afternoon tea
- Conference Dinner ticket
- Complimentary WIFI
- Tour of CSIRO's Lab 22, FloWorks and RAMP facilities

Registration Desk Opening Time

Monday 2 December 8:00am – 8:30am

Poster Session

The formal poster session is Monday at 6:00pm.

Conference Dinner

The Conference Dinner will be held in the Lake Rooms at the Pullman Albert Park from 7:30pm – 11:30pm. The Conference Dinner will include alternate 3 course meals and drinks.

Nametags

Delegates and registered partners are required to wear their nametags to all scientific and catered sessions.

WIFI

Complimentary WIFI is available for delegates within the conference areas for the duration of the conference. The WIFI connection is suitable for the viewing of emails and browsing. Downloading images and movies is not recommended.

The Activation Code is **CSIRO19**
02-03.12.19

To connect to the network, please follow the 7 easy steps below:

1. Turn on your Wireless device
2. Double click on your wireless icon in the bottom right hand tray
3. Select "Pullman Conference Wireless" unsecured wireless network
4. Select Visitor and enter code
5. Press connect
6. Launch your Internet Browser
7. Your browser will automatically be directed to our wireless network logon screen advising connection.

Special Meal Requests

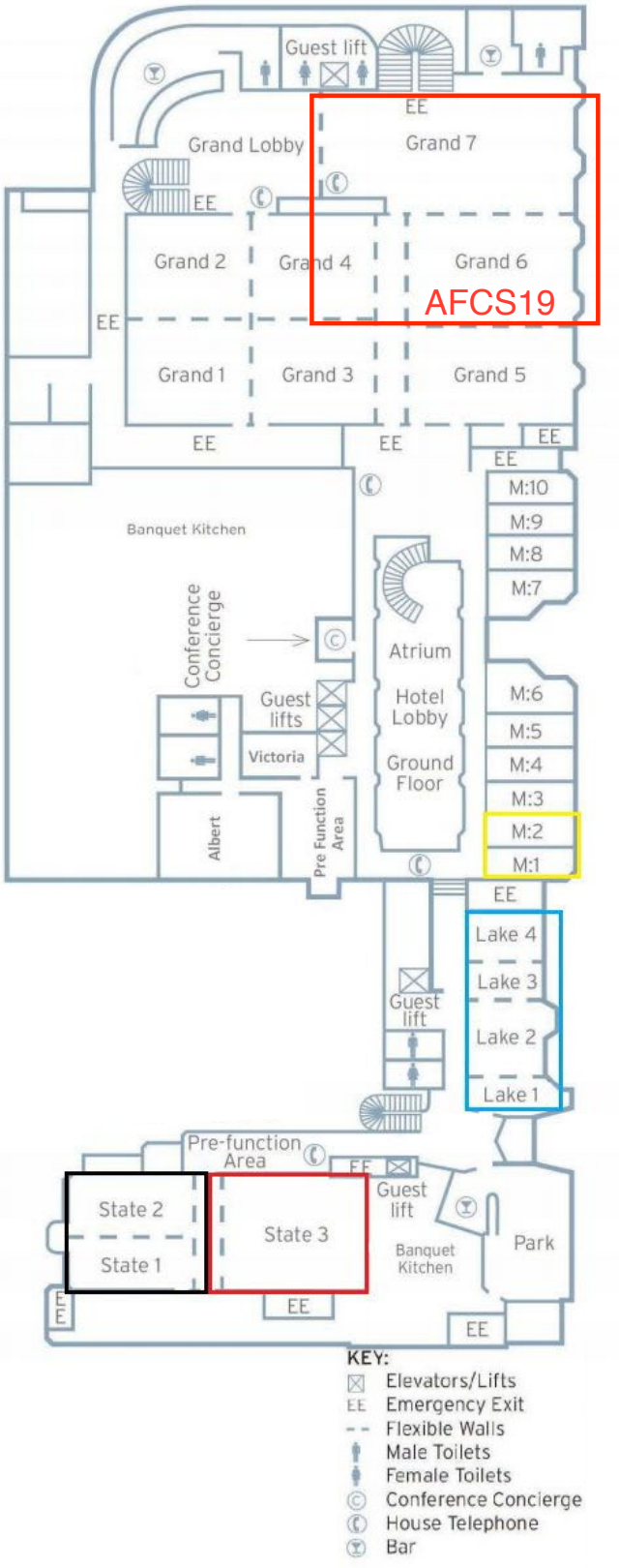
All dietary requirements have been passed on to the Pullman Albert Park Hotel. There will be a specific table which is just for those guests with a dietary requirement during breaks.

Please advise hotel staff at the dinner if you have specified any dietary needs.

Mobile Phones

Please ensure your mobile phone is turned to silent during any session you attend.

Conference and Event Centre



Program

Monday 2 December 2019

8:00am – 8:30am	**Registration and Opening of Exhibition**
8:30am – 9:00am	Welcome Address and Acknowledgment of traditional owners
Session 1	**Chair – Oliver Hutt, Boron Molecular**
9:00am – 9:50am	Plenary 1 – Shu Kobayashi, University of Tokyo – 'Toward Continuous Production of Fine Chemicals Using Flow Fine Synthesis'. *Sponsored by Boron Molecular*
9:50am – 10:30am	Keynote 1 – Karen Robertson, University of Nottingham – 'Controlling and monitoring crystallisation through flow technologies'. *Sponsored by Ehrfeld Mikrotechnik GmbH*
10:30am – 11:00am	**Morning Tea**
Session 2	**Chair – Tash Polyzos, CSIRO**
11:00am – 11:25am	Marcus Baumann, University College Dublin – 'Development of Continuous Flow Methods for Integrating Reactive Distillation and Photochemical Transformations'.
11:25am – 11:50am	Alessandra Vizza, Corning – 'Upgrading production capacity through inherently safer technology with Corning® Advanced-Flow™ Reactors for continuous manufacturing'.
11:50am – 12:15pm	Mike Horne, CSIRO Mineral Resources, Melbourne, Australia – 'Static Mixers, Dynamic Electrochemistry'.
12:15pm – 12:55pm	Keynote 2 – Hélène Lebel, University of Montreal – 'Novel Continuous Flow Synthetic Methods with Highly Reactive Intermediates'. *Sponsored by Cambridge Reactor Design Ltd*
12:55pm – 2:00pm	**Lunch**
Session 3	**Chair – Peter Bury, Chemistry Australia**
2:00pm – 2:50pm	Plenary 2 – Tanya Junkers, Monash University - Machine-Assisted Synthesis: Programmable Precision Polymers by the Push of a Button. *Sponsored by Innovative Manufacturing CRC Limited*
2:50pm – 3:15pm	Adam McCluskey – University of Newcastle – 'Bioactive scaffolds by flow'.
3:15pm – 3:40pm	Chris Gordon, University of Western Sydney – 'Immobilised Reagent Assisted Flow Chemistry'.
3:40pm – 4:10pm	**Afternoon Tea**
Session 4	**Chair – Christian Hornung, CSIRO**
4:10pm – 4:35pm	Manuel Nuno – Vapourtec, 'Use of advanced continuous flow reactors in organic synthesis. From electrochemistry to peptide synthesis.'
4:35pm – 5:00pm	Chinh Nguyen, Syrris – 'Segmented Flow Chemistry in Modern Compound Library Synthesis'.
5:00pm – 5:40pm	Keynote 3 – Volker Hessel, University of Adelaide – 'Flow Chemistry as Disruptive Technology in Space for Earth Industrial Transformation'. *Sponsored by Magritek*
6:00pm – 7:00pm	**Poster Session**
7:30pm – 11:30pm	**Symposium Dinner**

Tuesday 3 December 2019

8:30am – 9:00am	**Exhibitions**
Session 5	**Chair – Annabella Newton, Phillips Ormonde Fitzpatrick**
9:00am – 9:50am	Plenary 3 – C. Oliver Kappe, University of Graz – 'From flow chemistry in the lab towards industrial implementation on scale – case studies on continuous API synthesis'. *Sponsored by Phillips Ormonde Fitzpatrick*
9:50am – 10:15am	Anne Kaaden, Ehrfeld Mikrotechnik – 'Micro Reaction Technology as a pathway for future Production'.
10:15am – 10:40am	Oliver Hutt – Boron Molecular, 'Application of Flow Chemistry to Fine Chemical and Polymer Synthesis'.
10:40am – 11:15am	**Morning Tea**
Session 6	**Chair – James Gardiner, CSIRO**
11:15am – 11:40am	Charlotte Wiles – Chemtrix, 'Application of Continuous Flow Reactors for the Controlled Performance of Hazardous Processes – From R&D to Production'.
11:40am – 12:20pm	Keynote 4 – Tim Noel, Eindhoven University of Technology – 'Innovation in synthetic methodology through use of flow'. *Sponsored by FB Rice*
12:20pm – 12:40pm	**Closing and Awards**
12:40pm – 1:30pm	**Lunch**
1:30pm – 2:30pm	**Travel to Clayton by coach. Meet at front of hotel and check name off.**
2:30pm – 4:00pm	**CSIRO TOURS** • FloWork's state of the art flow chemistry laboratories; • Lab 22, metal additive manufacturing (3D printing) technologies; and • RAMP Rapid Automated Materials and Processing facility.
4:00pm – 5:00pm	**Return to Pullman Albert Park**

Speakers

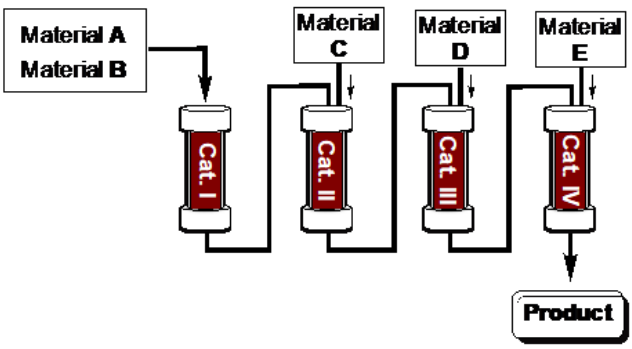
PLENARY SPEAKER

Shu Kobayashi

School of Chemistry, University of Tokyo, Tokyo, Japan

Toward Continuous Production of Fine Chemicals Using Flow Fine Synthesis

As a synthetic method, flow processes have several advantages over batch in terms of environmental compatibility, efficiency, and safety. Wastes derived from work-up processes can be minimized or omitted altogether by performing organic transformations in flow. Equipment for chemical manufacturing can be designed to be smaller, which would enable significant savings in space and costs. In addition, the differences between batch and flow reactors, which are the large surface to volume ratios and the rapid mixing/quenching of reagents, should make chemical productions safer and more efficient. While continuous-flow practices have been adopted in the petrochemical and bulk chemical industries, its application in fine chemical production is limited. It was believed that synthesis by flow methods could be applicable for the production of simple gasses such as ammonia, but was difficult to apply to the preparation of complex molecules such as active pharmaceutical ingredients (APIs). This lecture will discuss recent advances in organic synthesis enabled by continuous-flow methods. In particular, the development of heterogeneous catalysts in multi-step continuous-flow reactions (sequential-flow reactions) for the synthesis of complex organic molecules will be highlighted.



PLENARY SPEAKER

Tanja Junkers

a School of Chemistry, Monash University, Melbourne, Australia
b Institute for Materials Research, Hasselt University, Hasselt, Belgium

Machine-Assisted Synthesis: Programmable Precision Polymers by the Push of a Button

Contemporary macromolecular chemistry has matured to a point where virtually any polymer structure can be synthesized via combinations of controlled polymerization approaches, postpolymerization modification and efficient ligation strategies. Still, often large hurdles have to be overcome to take the next step in research, that is being able to provide such complex materials reliably on significant scale for use in advanced applications. A solution to this problem is to make use of continuous flow synthesis techniques. Flow reactors are associated with high reproducibility, intrinsically simple reaction scale-up and improved product qualities due to significant reduction of side reactions. Being an established method especially in the pharmaceutical chemistry domain, full potential with regards to macromolecular synthesis did not unfold until very recently. Among others, the benefits of using online-monitoring will be discussed and the development of fully autonomous machine-learning based reactor systems presented.

On the example of a variety of thermal and photochemically induced polymerizations, the potential of machine-learning in combination with flow chemistry will be highlighted. Specifically, the unmatched precision with respect to monomer conversion and average molecular weight that can be reached in self-optimizing reactor systems is elucidated. Various first applications of such systems will be shown. Among others, the ability to produce materials with an artificial molecular weight distribution opens new avenues in material design that classical approaches cannot provide. Applications in this realm stretches from precision thermal and mechanical material properties design to information encoding.

PLENARY SPEAKER

C. Oliver Kappe

Center for Continuous Flow Synthesis and Processing (CC FLOW), Research Center Pharmaceutical Engineering GmbH (RCPE), Graz, Austria
Institute of Chemistry, University of Graz, NAWI Graz, Graz, Austria
oliver.kappe@uni-graz.at // http://goflow.at

From flow chemistry in the lab towards industrial implementation on scale – case studies on continuous API synthesis.

Continuous flow processes form the basis of the petrochemical and bulk chemicals industry where strong competition, stringent environmental and safety regulations, and low profit margins drive the need for highly performing, cost effective, safe and atom efficient chemical operations. In contrast to the commodity chemical industry, however, the fine chemical industry primarily relies on its existing infrastructure of multipurpose batch or semi-batch reactors. Fine chemicals, such as drug substances and active pharmaceutical ingredients (APIs), are generally considerably more complex than commodity chemicals and usually require numerous, widely diverse reaction steps for their synthesis. These requirements generally make versatile and reconfigurable multipurpose batch reactors the technology of choice for their preparation.

However, the advantages of continuous flow processing are increasingly being appreciated also by the pharmaceutical industry and, thus, a growing number of scientists, from research chemists in academia to process chemists and chemical engineers in pharmaceutical companies, are now starting to employ continuous flow technologies on a more routine basis. In this lecture, contributions from our research group in the field of continuous flow processing will be highlighted. Emphasis will be given to highly atom efficient and process intensified chemical transformations useful for the synthesis of APIs or key intermediates that are often too hazardous to be executed in a batch reactor. These involve azide, diazomethane and nitration chemistry, selective precious metal-free olefin and nitrogroup reductions, oxidation reactions involving pure oxygen, and flow photochemistry applications. Special emphasis will be given to the scalability issues and industrial collaboration with both pharma companies and CMOs and equipment/technology providers.

KEYNOTE SPEAKER

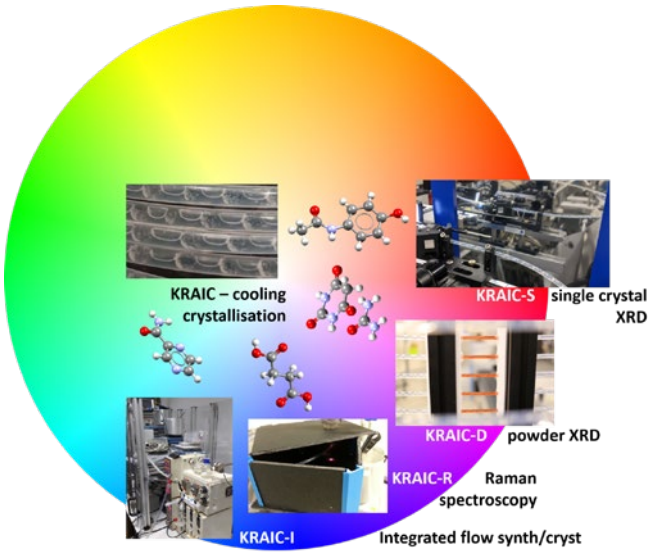
Karen Robertson

Faculty of Engineering, University of Nottingham, Nottingham, United Kingdom

Controlling and monitoring crystallisation through flow technologies

Flow technologies in academic laboratories have been almost exclusively been the reign of liquids and gases since inception. The complications of handling solids in flow environments has severely retarded the uptake of flow technologies in applications which use or produce solids. Flow crystallisation is a branch which, through a combination of traditional industrial scaling and using high velocities to overcome sedimentation, is typically outside the parameters of compatibility with traditional academic laboratory flow synthesis. We have applied a tri-segmented approach to overcome both the challenges of sedimentation and how to couple flow synthesis with crystallisation.

The evolution of a series of flow crystallisers will be presented ranging from pure cooling crystallisation, through integrated flow synthesis and crystallisation to in situ analysis via Raman spectroscopy and both powder and single crystal X-ray diffraction. These crystallisers have been commissioned to control, monitor and understand crystallisation events including the promotion of unusual polymorphic forms and elucidation of polymorphic stability. Case studies from the production of pharmaceutical compounds such as succinic acid, pyrazinamide and the co-crystalline urea : barbituric acid will be presented.



Speakers

KEYNOTE SPEAKER

Volker Hessel

University of Adelaide, ECMS Faculty, Adelaide, Australia

Flow Chemistry as Disruptive Technology in Space for Earth Industrial Transformation

Volker Hessel[a], Daniel Kinasz[a], Olivia Zeckovic[b], Mahdieh R. Asrami[a], Sanaz Orandi[a], Nam N. Tran[a], John Culton III[a], Michael Goodsite[a], Hung Nguyen[a], Jana Stoudemire[c]

a University of Adelaide, ECMS Faculty, North Terrace, Adelaide, 5005, Australia

b University of Queensland, School of Biomedical Sciences, Chancellors Pl, St Lucia, Brisbane, 4072, Australia.

c Space Tango, 611 Winchester Rd, Lexington, KY 40505, U.S.A.

Chemical processing in Space happens every day (on ISS, 250 miles above) and that includes flow chemistry and microfluidics. Rather than using advantage as vantage point, as satellites do, in-space manufacturing utilises microgravity as central innovation point, and biology/organoids/tissues give rise to the first business cases in Space. The NASA Administrator Bridenstine referred to in-space manufacturing as an “absolute game-changer” for the agency.

Space exploration raises, however, also sustainability concerns (eg Space debris). So we need Green Chemistry in Space.

Disruptive Technologies have potential for industrial transformation, and can raise green chemistry impact in step change mode. Recent example is the use of continuous-flow for industrial pharmaceutical manufacture, endorsed by the industry stakeholders and FDA.

The new forefront and frontier for disruptive technologies is Space, in particular concerning the coming planetary missions (Moon, Mars). Continuous-flow technology is commonly acclaimed as prime Space chemical manufacturing technology, as they effectively work (already on Earth) under microgravity, are encased process units with no headspace, are low-weight, and have large promise for automation [1].

Their disruptive nature will be demonstrated at several space applications: (1) selective solvent extraction of Co vs Ni in flow from mimicked asteroid/planetary ores (2) phosphate leaching from mimicked moon crusts, and (3) process design for medicine manufacture on moon ground and a mapping for excipient resources on moon to produce the “tablet out of moon dust”.

The potential of own-developed recent process intensification concepts (for Earth manufacturing) to induce those disruptive changes in Space will be assessed [2]: novel process windows (eg high-p,T), ‘master-solvent enabled factory’, ‘fertilising with wind’, etc.

That assessment is meant to provide first ideas on sustainability and green chemistry in Space. This includes the proposition of out-of-box concepts such as use of lunar-abundant materials, lunar circular economy (resource accumulation in plants and use those for basic organic materials), (near-)zero solvent processing, and supply chains determined by environmental constraints; besides a throughout use of solar energy. Is there a new Green Chemistry in Space?

1. Jones, R.; Darvas, F.; Janáky, C. Nat. Rev. Chem. 2017, 1, article number: 0055
2. Hessel, V: Tran, N. N.; Orandi, S.; Asrami, M. A.; Goodsite, M.; Nguyen, H. submitted. 2019.

KEYNOTE SPEAKER

Helene Lebel

Centre in Green Chemistry and Catalysis, Department of Chemistry, Université de Montréal, Montréal, Québec, Canada

Novel Continuous Flow Synthetic Methods with Highly Reactive Intermediates.

Continuous flow technology offers many advantages, including the safe manipulation of highly reactive intermediates. The Lebel group has been particularly interested in the use of this strategy for synthesis of diazo compounds and to study the reactivity of aliphatic diazoniums. Diazoniums can be in-situ generated from an amine and a nitrite reagent in the presence of an acid. The trapping of aliphatic diazoniums with carboxylates, electron rich aromatics and other nucleophiles afforded various synthetic compounds in high yields. Furthermore, the Lebel group has developed novel precursors to form metal nitrene species that undergo C–H amination, aziridination as well as thioether and sulfoxide amination reactions. New continuous flow processes for amination reactions will be described in this presentation.

KEYNOTE SPEAKER

Tim Noel

Department of Chemical Engineering and Chemistry, Micro Flow Chemistry and Synthetic Methodology, Eindhoven University of Technology, Eindhoven, The Netherlands

Innovation in synthetic methodology through use of flow

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]

My 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], C–H activation chemistry[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.

1. (a) H. P. L. Gemoets, Y. Su, M. Shang, V. Hessel, R. Luque, T. Noel, Chem. Soc. Rev. 2016, 45, 83-117. (b) D. Cambie, C. Bottecchia, N. J. W. Straathof, V. Hessel, T. Noel, Chem. Rev. 2016, 116, 10276-10341.
2. (a) X.-J. Wei, W. Boon, V. Hessel, T. Noel, ACS Catal. 2017, 7, 7136-7140. (b) C. Bottecchia, M. Rubens, S. Gunnoo, V. Hessel, A. Madder, T. Noel, Angew. Chem. Int. Ed. 2017, 56, 12701-12707. (c) D. Cambie, F. Zhao, V. Hessel, M. G. Debije, T. Noel, Angew. Chem. Int. Ed. 2017, 56, 1050-1054. (d) N. J. W. Straathof, S. E. Cramer, V. Hessel, T. Noel, Angew. Chem. Int. Ed. 2016, 55, 15549-15553.
3. (a) G. Laudadio, S. Govaerts, Y. Wang, D. Ravelli, H. F. Koolman, M. Fagnoni, S. W. Djuric, T. Noel, Angew. Chem. Int. Ed. 2018, 57, 4078-4082.. (b) H. P. L. Gemoets, G. Laudadio, K. Verstraete, V. Hessel, T. Noel, Angew. Chem. Int. Ed. 2017, 56, 7161-7165. (c) U. K. Sharma, H. P. L. Gemoets, F. Schoeder, T. Noel, E Van der Eycken, ACS Catal. 2017, 7, 3818-3823.
4. (a) G. Laudadio, W. De Smet, L. Struik, Y. Cao, T. Noel, J. Flow Chem. 2018, 8, 157-165. (b) G. Laudadio, N. J. W. Straathof, M. D. Lanting, B. Knoops, V. Hessel, T. Noel, Green Chem. 2017, 19, 4061-4066.

Invited speakers

Marcus Baumann

School of Chemistry, University College Dublin, Dublin, Ireland

Development of Continuous Flow Methods for Integrating Reactive Distillation and Photochemical Transformations

Continuous flow chemistry has matured into a widely recognised enabling technology through the development and dissemination of various key applications from both industry and academia. More recently this also encompasses the integration of in-line analysis and purification techniques to bring about the effective multi-step synthesis of valuable target compounds. From this it is apparent that powerful continuous processes can be realised through the full integration of a variety of important tools to serve both the chemical synthesis of valuable entities as well as their purification and analysis.

In this talk we will highlight our recent work in the field of continuous flow chemistry, specifically the development of hybrid flow approaches that integrate reactive distillation methods with continuous cycloaddition reactions. This will be highlighted by showcasing how the safe generation of cyclopentadiene from its dimeric precursor can be accomplished in a continuous fashion This process is coupled with an indium catalysed Povarov cycloaddition reaction to yield drug-like heterocyclic architectures without exposure of the operator to the obnoxious cyclopentadiene intermediate.

Additionally, a selection of new continuous photochemical transformations will be discussed that demonstrate the advantageous nature of flow-based processing that enables the generation of different drug-like entities. As photochemical approaches are not readily scaled when using conventional batch techniques, such continuous photochemical routes open new avenues towards a multitude of important transformations that render the desired products in a highly atom-economical and oftentimes expedited fashion.

Alessandra Vizza

Reactor Technologies, Corning SAS, Avon, France
E-mail: vizzaa@corning.com

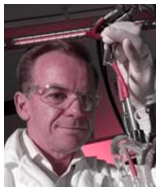
Upgrading production capacity through inherently safer technology with Corning® Advanced-Flow™ Reactors for continuous manufacturing

This talk will highlight how continuous flow reactors have been successfully applied in a variety of processes including examples of applications where hazardous reactions or extreme process conditions have been used. Areas that stretch into the future and will be critical to secure the upcoming of safe chemical industry productions will be presented. Some industrial installations are presented to demonstrate that continuous production is a reality, reflecting the reliability of the Corning® Advanced-Flow™ Reactors and market confidence.

Mike Horne

CSIRO Mineral Resources, Melbourne, Australia

Static Mixers, Dynamic Electrochemistry



Mass transport is a key factor that influences electrochemical processing. The transport of reactants to a surface and products back into bulk solution limits the efficiency with which metals are recovered and refined, batteries are charged and discharged, gases are generated, materials are synthesised, and pollutants and pathogens are destroyed. Mixing is particularly important for electrochemical processing because redox reactions involve electron tunnelling, requiring the reactant to be within about 1 nm of the electrode and reside there long enough for the rate of reaction to be acceptably high. When dilute solutions are processed, this requirement means traditional stirred batch reactors may take many hours or days to complete a reaction.

CSIRO has devised a flow electrochemical cell in which the working electrode is an additively manufactured static mixer. At modest pump speeds this cell accelerates the rate of diffusion limited reactions by up to 40 times, providing a powerful technology for facilitating a range of processes including the removal of heavy metal pollutants, water disinfection, gas generation and some key electrosynthetic procedures.

The design rationale underpinning the cell and its performance are described in this talk.

Adam McCluskey

Chemistry, School of Environmental & Life Sciences,
The University of Newcastle, Newcastle, NSW, Australia

Bioactive Scaffolds by Flow

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 bioactive compounds spanning and array of biological targets.1-3

1 Hizartzidis L, Gordon CP, Gilbert J, Sakoff JA, McCluskey A. Synthesis of Chimeric norcantharidin phenylacrylonitrile cytotoxic compounds. ChemMedChem., 14 (2019) 1152-1161.

2 Luwor R, Morokoff AP, Amiridis S, D'Abaco G, Paradiso L, Stylli SS, Nguyen HPT, Tarleton M, Young KA, O'Brien TJ, Robinson PJ, Chircop M, McCluskey A, Jones NC. Targeting Glioma Stem Cells by functional inhibition of Dynamin 2: a novel treatment strategy for Glioblastoma, Cancer Investigation, 37 (2019) 144-155.

3 Gilbert J, De Illius GN, Tarleton M, McCluskey A, Sakoff JA. (Z)-2-(3,4-Dichlorophenyl)-3-(1H-Pyrrol-2-yl)Acrylonitrile Exhibits Selective Antitumor Activity in Breast Cancer Cell Lines via the Aryl Hydrocarbon Receptor Pathway. Molecular Pharmacology 93 (2018) 168-177.

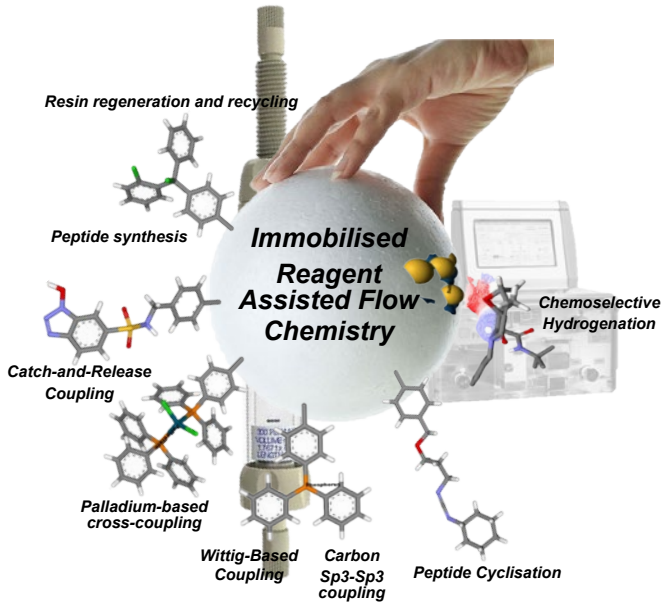
Invited speakers

Christopher P. Gordon

School of Science and Health, Western Sydney University, Penrith South, NSW, Australia

Immobilised Reagent Assisted Flow Chemistry

While the concept of solid-phase assisted synthesis was initially devised for the assembly of peptide sequences,[1] the technique has since been widely adopted throughout the chemical industry with immobilised reagents employed as anchors, catalysts, reagents, and scavengers. Further, it is becoming increasingly apparent that the advantages provided by immobilised species have only been partially realised through their application in batch-based chemistries. Indeed, it is becoming apparent that additional gains are attainable when these agents are integrated into flow-based synthetic protocols.[2-4] Using combinations of fixed-bed catalysts, immobilised reagents, and solid-phase synthesis resins, we have focused on developing convenient flow-based protocols to effect a number of widely utilised chemical transformations. Here we describe a number of these protocols including phosphine-mediated C(sp3)–C(sp3) coupling,[5] chemoselective olefin hydrogenation,[6-9] biaryl cross-coupling,[10] and the total synthesis of cyclic peptides synthesis.[11-12]



1 Merrifield, R. B., Solid phase peptide synthesis. I. The synthesis of a tetrapeptide. J. Am. Chem. Soc. 1963, 85 (14), 2149-54.

2 Baumann, M.; Baxendale, I. R., The synthesis of active pharmaceutical ingredients (APIs) using continuous flow chemistry. Beilstein Journal of Organic Chemistry 2015, 11, 1194-1219.

3 de Miguel, Y. R.; Brule, E.; Margue, R. G., Supported catalysts and their applications in synthetic organic chemistry. J. Chem. Soc., Perkin Trans. 1 2001, (23), 3085-3094.

4 Baxendale, I. R.; Ley, S. V., Solid supported reagents in multi-step flow synthesis. Ernst Schering Foundation Symposium Proceedings 2007, (2006-03, New Avenues to Efficient Chemical Synthesis), 151-185.

5 Tran, U. P. N.; Hock, K. J.; Gordon, C. P.; Koenigs, R. M.; Nguyen, T. V., Efficient phosphine-mediated formal C(sp3)-C(sp3) coupling reactions of alkyl halides in batch and flow. Chem. Commun. (Cambridge, U. K.) 2017, 53 (36), 4950-4953.

6 Hizartzidis, L.; Gilbert, J.; Gordon, C. P.; Sakoff, J. A.; McCluskey, A., Synthesis and Cytotoxicity of Octahydroepoxyisoindole-7-carboxylic Acids and Norcantharidin-Amide Hybrids as Norcantharidin Analogues. ChemMedChem 2019, Ahead of Print.

7 Spare, L. K.; Harman, D. G.; Aldrich-Wright, J. R.; Nguyen, T. V.; Gordon, C. P., Chemoselective Flow Hydrogenation Approaches to Diversify the Cytotoxic Tetrahydroepoxyisoindole Carboxamide Scaffold. Adv. Synth. Catal. 2018, 360 (6), 1209-1217.

8 Hizartzidis, L.; Tarleton, M.; Gordon, C. P.; McCluskey, A., Chemoselective flow hydrogenation approaches to isoindole-7-carboxylic acids and 7-oxa-bicyclo[2.2.1]heptanes. RSC Adv. 2014, 4 (19), 9709-9722.

9 Hizartzidis, L.; Cossar, P. J.; Robertson, M. J.; Simone, M. I.; Young, K. A.; McCluskey, A.; Gordon, C. P., Expanding the utility of flow hydrogenation - a robust protocol restricting hydrodehalogenation. RSC Adv. 2014, 4 (100), 56743-56748.

10 Trinh, T. N.; Hizartzidis, L.; Lin, A. J. S.; Harman, D. G.; McCluskey, A.; Gordon, C. P., An efficient continuous flow approach to furnish furan-based biaryls. Org. Biomol. Chem. 2014, 12 (47), 9562-9571.

11 Spare, L. K.; Menti, M.; Harman, D. G.; Aldrich-Wright, J. R.; Gordon, C. P., A continuous flow protocol to generate, regenerate, load, and recycle chlorotrityl functionalised resins. Reaction Chemistry & Engineering 2019, 4 (7), 1309-1317.

12 Spare, L. K.; Laude, V.; Harman, D. G.; Aldrich-Wright, J. R.; Gordon, C. P., An optimised approach for continuous-flow solid-phase peptide synthesis utilising a rudimentary flow reactor. Reaction Chemistry & Engineering 2018, Ahead of Print.

Manuel Nuno

Research Scientist, Vapourtec Ltd, Suffolk, United Kingdom

Use of advanced continuous flow reactors in organic synthesis. From electrochemistry to peptide synthesis

Terpenes, such as valencene, are low cost, natural products which can modified into ketones, with more added value, following conventional chemical routes involving heavy metals, such as chromium.

Although electrochemistry was discovered in 1800 with the creation of the voltaic pile, the limitations of batch chemistry have been restricting its wide use by synthetic chemists. Vapourtec has recently developed the Ion Electrochemical Reactor, which takes advantage of the extremely large surface-to-volume ratios that a flow microreactor provides to make selective oxidation of terpenes. This is viable under mild chemical conditions using either air or oxygen as the source of O2. By way of example this talk shows the optimisation undertaken in the oxidation of Valencene to Nootkatone.

C-H activation has been a topic of study since H. J. Fenton reported his findings in 1894. Since then, organic chemists have been using organocatalysis to functionalise C-H bonds. It often requires the need of prefunctionalised starting materials to carry such activation. In recent years, the development of photoinduced processes have witnessed great progress with regards to photocyclisations and photocatalysed C-H functionalisation reactions. The limiting factor on these reactions is usually the photon density that irradiates the reagents. With the use of the newly developed 150W UV LED, we report the effect of photon density on 2+2 photocyclisation reactions.

The final part of the talk will focus on solid-phase peptide synthesis in flow. Although SPPS is a well-established technique, the lack of live inline data can lead to several problems, such as an incomplete peptide and waste of reagents. By recording the volume change in a variable bed flow reactor and, combined with an inline UV detector, Vapourtec's team was able to evaluate difficult couplings and develop optimised conditions.

Chinh Nguyen

Flow Chemistry Specialist, Syrris Ltd

Exploiting segmented flow chemistry in modern compound library synthesis

The pharmaceutical industry continues to go through changes both in its approach to drug discovery and in the way, it uses new enabling technologies. The constant demand to deliver new drugs to market is the driver to adopt new strategies to improve the speed through early discovery to production and to the point of care. One of the major challenges faced today in drug discovery programs is the increasing demand to deliver a continuous supply of active compounds, generally novel and structurally diverse, in increasing numbers and in shorter timelines. The use of continuous flow technology in the chemical synthesis of libraries allows the exploration of novel reaction windows to deliver a wider chemical space and more compound diversity over traditional methods. The technique enables the rapid optimization of synthetic protocols, access to reactions that were formerly avoided because of scale or safety concerns, telescoped reactions avoiding purification between steps and ready-made scale-up strategies. This presentation illustrates how flow chemistry technology has enabled the synthesis of a range of structurally diverse compounds across a range of chemistries with the benefits of automation and reaction control.

Invited speakers

Anne Kaaden

Head of Marketing, Ehrfeld Mikrotechnik GmbH, Wendelsheim, Germany

Micro Reaction Technology as a pathway for future Production Multi-Ton Production Millireactor replaces traditional Batch Reactors

During the past 20 years, micro reaction technology raised from a pure academic field of research to a technology which can be used in the industrial area of the chemical and pharmaceutical industry. The most important benefits like the higher heat exchange, better mixing leading to higher yields are based on a higher surface to volume ratio in comparison to traditional batch technology. Nevertheless, this technology suffers from a broader acceptance as a process technology within these industries. These concerns are mainly driven by unforeseen risk difficulties from this new technology due to a lack of visible reference projects in production scale.

Beneficial market segments will be presented for a successful use of this technology, the scale up strategy from first lab experiments to an industrial scaled reactor. Hereby, the focus is always related to an improvement of the process and economic efficiency, presented for several examples, in comparison to traditional batch processes.

Additionally, we will present a reference project for an attractive chemical reaction in a millireactor with a capacity of 10,000 t/a year. Furthermore, the savings in energy, footprint, personal and in the demand of raw material as well as the downstream process will be shown.

Oliver Hutt

Boron Molecular, Noble Park, Melbourne, Australia

Application of Flow Chemistry to Fine Chemical and Polymer Synthesis

Over the last 5 years Boron Molecular has developed and successfully commercialised multiple flow chemistry processes in partnership with the CSIRO. These processes range from discreet small molecules through to niche polymers and metal-organic-frameworks. This presentation will provide an overview of the product portfolio derived from flow chemistry and the impact these processes are having on Boron Molecular's ability to bring novel products to market.

Charlotte Wiles

Chemtrix BV, Echt, The Netherlands

Application of Continuous Flow Reactors for the Controlled Performance of Hazardous Processes - From R&D to Production

A series of industrial case studies will be used to illustrate the way various companies have approached going from considering continuous flow as a research tool through to manufacturing using the technique. The presentation will show that a multidisciplinary approach is required to achieve these goals as projects transition from the chemists' domain to one led by chemical and mechanical engineers.

The presentation will also touch on the need for modularity, robust materials of construction, scalable reaction control & standardization when implementing continuous processing for primary processing of small molecules.

Poster abstracts

Jose Augusto Forni
University of Melbourne, Australia

Visible-Light Promoted Tandem Photoredox Catalysis: Enabling Aminocarbonylation of Unactivated Alkyl Iodides in Continuous Flow.

Jennifer Baker
University of Newcastle, Australia

Knoevenagel condensation by flow: solid-supported catalysts

Bita Bayatsarmadi
CSIRO Manufacturing, Melbourne, Australia

Intensifying Diffusion-Limited Reactions by Using Static Mixer Electrodes in a Novel Electrochemical Flow Cell

Axel-Laurenz Buckinx
Monash, University, Australia

Kinetic Control of Aggregation Shape in Micellar Self-Assembly Using Flow Reactors

Damian Fullston
CSIRO Manufacturing, Melbourne, Australia

Autonomous Macromonomer Production with Flow Chemistry

James Gardiner
CSIRO Manufacturing, Melbourne, Australia

Bio-CSMs: Enzyme-Coated Static Mixers for Continuous Biochemical Processing

Continuous Flow Hydrogenations using Catalytic Static Mixers: Application to a Key Pharmaceutical Intermediate of Linezolid (Zyvox™).

Carol Hartley
CSIRO Land and Water, Canberra, Australia

Nanomachine Biocatalysts: Tools for continuous flow biocatalysis

Brandon He
Monash University, CSIRO

Efficient Synthesis of Multicomponent Metal-Organic Frameworks

Ioli C. Howard
University of Bath, United Kingdom

The Application of Homogeneous and Heterogeneous Ring-Opening Polymerisation into Flow

Tom Kohl
CSIRO Manufacturing, Melbourne, Australia

Polyaniline on Tap

Edward Phung
University of Melbourne, Australia

Multistep Synthesis of Benzhydrylamines via Photoredox Catalysed Transfer Hydrogenation in Continuous Flow

Nikolai Piers Rossouw
University of Melbourne, Australia

Towards the Continuous Flow Synthesis of Alkyl Citrate Natural Products

Rowan Pilkington
CSIRO Manufacturing, Melbourne Australia

Organocatalytic Decarboxylation of Amino Acids in Continuous Flow: A Scalable Route to 3-Hydroxypyrrolidine

Maarten Rubens
University of Hasselt, Hasselt, Belgium

Absolute control over molecular weight distributions through autonomous polymer synthesis

Dean van As
University of Melbourne, Australia

The Visible Light Mediated Radical Decarboxylative α-Alkylation of Amines in Continuous Flow

Joren Van Herck
Monash University, Melbourne Australia

Automated Polymer Synthesis Platform for Integrated Conversion Targeting Based on Inline Benchtop NMR

Charlotte Williams
CSIRO Manufacturing, Melbourne, Australia

Nanomachine Biocatalysts: multi-enzyme cascades for sustainable industrial chemistry

FloWorks

Australia's Centre for Industrial Flow Chemistry

CSIRO's FloWorks Centre for Industrial Flow Chemistry provides Australian and international chemical manufacturers with access to CSIRO's cutting-edge research into industrial processing. FloWorks is located in the heart of the Australian Manufacturing and Materials Precinct in Clayton, and comprises a purpose-built 410 m^2 pilot scale foundry available for industry and research bodies to partner and develop flow chemistry processes.

The centre has significant capability in flow chemistry as a key driver of process intensification, and its state-of-the-art laboratories house the continuous flow reactors and ancillary chemical process equipment needed to address all stages of the R&D pipeline from discovery to process development and scale-up (pilot and industrial).

Our world-class researchers can provide a range of different services depending on a client's needs, including process R&D operations; managing technology transfer to a client's site; and in-house training for industrial collaborators on the centre's flow chemistry and process equipment.

As Australia's national science agency and innovation catalyst, CSIRO is solving the greatest challenges through innovative science and technology.

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B&M | 19-00537

Knoevenagel condensation by flow: solid-supported catalysts

Jennifer R Baker,[1] Cecilia Russell,[1] Phuoc Nguyen,[1] Levena Gascoigne,[1] Nicholas Cain,[1] and Adam McCluskey[1]

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The Knoevenagel condensation occurs between a compound with an activated methylene carbon and an aldehyde. Typically catalyzed by an organic base such as piperidine or pyridine, the reaction continues to have great importance for C-C bond formation.[1,2]

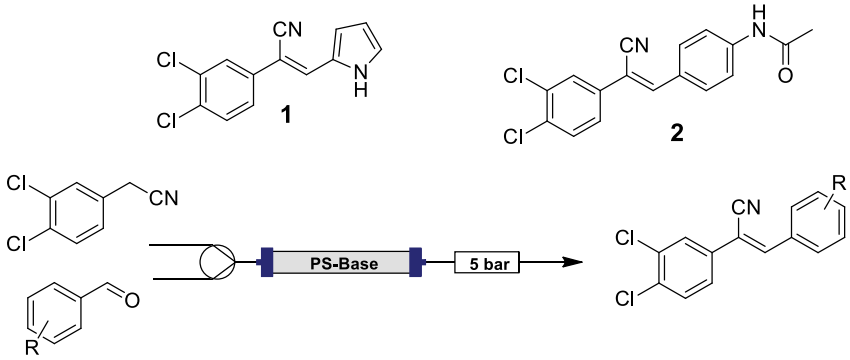
Ongoing projects in our group include the development of small molecule activators of the Arylhydrocarbon Receptor (AhR) pathway, for the treatment of breast cancer.[3] Two compounds that have come out of these studies, ANI-7 (**1**) and its 4-acetamide phenyl derivative (**2**), are both afforded via the Knoevenagel condensation.

We sought to convert this reaction to a flow platform for easy library synthesis. Our aim was that the generation of compounds could be conducted by undergraduate students, with minimal research lab experience.

Initial attempts to convert this reaction to a flow protocol was unsatisfying due to the high equivalents of piperidine required.[4] As such, we sought to explore the preparation and use of a number of organic bases on a silica medium. The use of solid-supported catalysts in flow reactors is well published, and demonstrates many benefits over a homogenous catalyst in solution.[5]

Our requirements were that these heterogenous catalysts were able to be prepared from cheap, readily available starting materials; that their preparation be relatively quick, with little work up required; and that the catalyst be reusable. These requirements ensured that, should the catalyst be exhausted, it could be resynthesized quickly, easily and cheaply. As these solid-supported catalysts would be utilized by undergraduate students, it was essential that their preparation involved mild conditions, and that they were able to be quickly and cheaply prepared. A number of established protocols were utilized,[6-8] as well as some novel syntheses.

Here we report the synthesis of five different silica-supported organic bases, and their use for the synthesis, in a flow instrument, of new ligands for the AhR pathway.



References

[1] List et al., *Angew. Chem. Int. Ed.* **2010**, *49,* 1730-1734.
[2] Khare et al., *Orient. J. Chem.* **2019**, *35*, 423-429.
[3] Baker et al., *ChemMedChem*. **2018**, *13*, 1447-1458.
[4] Cain et al., unpublished work.
[5] Prota et al., *Org. Process Res. Dev.* **2016**, *20*, 2-25.
[6] Zaoui et al., *Sci. Study & Res.* **2017**, *18*, 1-8.
[7] Ribero et al., *Applied Catalysis A: General.* **2011**, *399*, 126-133.
[8] Shanmuganathan et al., *Tetrahedron Letters.* **2010**, *51*, 6670-6672.

Intensifying Diffusion-Limited Reactions by Using Static Mixer Electrodes in a Novel Electrochemical Flow Cell

Bita Bayatsarmadi, Mike Horne, Miao Chen, Theo Rodopoulos

Surface-mediated reactions require effective mixing for them to be intense and efficient. In electrochemistry where the reactants must contact electrode surfaces for a sufficient time to enable electron tunnelling to occur, exhaustive electrolysis in poorly stirred reactors can take many hours to complete. As a consequence, electrochemical processing in many industries is restricted to batch processing which is more costly and labour intensive than continuous processing and results in significant down time between batches. This is not ideal for bulk production or treatment. Here we describe CSIRO's novel axial flow electrochemical cell which aims to address these mixing problems by using a bespoke static mixer electrode (SME), designed by computational fluid dynamics (CFD) and manufactured using additive manufacturing technology to retain the fidelity of the original design. This electrode was characterized by SEM-EDS and electrosorption measurements. The performance of the electrochemical flow cell was evaluated by probing the ferricyanide ($[Fe(CN)_6]^{3+}$) reduction reaction on a platinum-coated SME under controlled mass transport conditions using cyclic voltammetry (CV), linear sweep voltammetry (LSV) and chronoamperometric measurements. Results affirm that the ferricyanide reduction rate is increased significantly in the novel CSIRO flow electrochemical cell, particularly in dilute solutions ($<10^{-2}$ M) where mass transport by diffusion plays a significant role. The performance of the cell is compared with a rotating disk electrode and a tubular flow cell.

Kinetic Control of Aggregation Shape in Micellar Self-Assembly Using Flow Reactors

Axel-Laurenz Buckinx,[1] Kirsten Verstraete,[2] Evelien Baeten,[2] Rico Tabor,[3] Anna Sokolova,[4] Neomy Zaquen,[2] Tanja Junkers[1,2]

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The kinetic and thermodynamic processes by which amphiphilic block copolymers (BCPs) self-assemble into nanostructures has been used extensively over the past decades. BCPs can self-assemble into different morphologies such as micelles, vesicles and rods, which have been proven to have a considerable influence in cell-uptake. This process of self-assembly is governed by complex thermodynamic factors such as repulsion of solubilized chains in the hydrophilic corona, stretching of hydrophobic chains in the core and interfacial tensions.[1] However, it remains nontrivial to precisely predict the morphology after self-assembly of amphiphilic BCPs.

Utilizing the benefits of flow chemistry, kinetic control towards micelle shape is investigated using static micromixers and varying flowrates for the aqueous and organic phase.[3] This method allows for micelles to be made with the same block copolymer into ellipsoids (130 nm/33 nm) at low mixing speed to near spherical particles (44 nm /26 nm) solely by altering flowrates of the two phases as shown by small angle neutron scattering (**Figure 1)**. This platform is a first step towards further investigation on morphology control of self-assembled nanostructures using a top-down approach, which will have a significant impact on a plethora of existing drug-delivery applications.

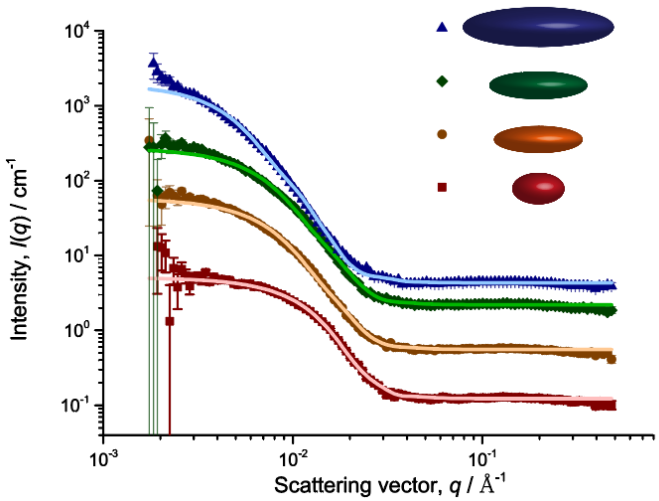

Figure 1. Small-angle neutron scattering data from $PHEA_{30}$-*b*-PS_{100} with a D2O background subtracted (symbols) and theoretical fits (solid lines) of micelles self-assembled at different flow rates. Blue=1mL·min^{-1}, Green=2mL·min^{-1}, Orange=4mL·min^{-1} and Red=8mL·min^{-1}

[1] Y. Mai, A. Eisenberg, *Chem. Soc. Rev.* **2012**, *41*, 5969-5985.
[2] B. Karagoz, L. Esser, H. T. Duong, J. S. Basuki, C. Boyer, T. P. Davis, *Pol. Chem.* **2014**, *5*, 350-355.
[3] *A.-L. Buckinx, K. Verstraete, E. Baeten, R. F. Tabor, A. Sokolova, N. Zaquen, T. Junkers, Angew. Chem. Int. Ed.* ***2019****, 58, 13799.*

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Personal History:

2015-2017	MSc. Bioelectronics and Nanotechnology, Hasselt University
Since 2018	Ph. D. Chemistry, Monash University Research interests: Polymer
Research interests:	Polymers, Self-Assembly, Nanoparticles

Visible-Light Promoted Tandem Photoredox Catalysis: Enabling Aminocarbonylation of Unactivated Alkyl Iodides in Continuous Flow.

José A. Forni [a], Geethika Weragoda[b], Timothy U. Connell[c], Anastasios Polyzos[a], [b]

[a]*School of Chemistry, The University of Melbourne, Parkville, VIC*

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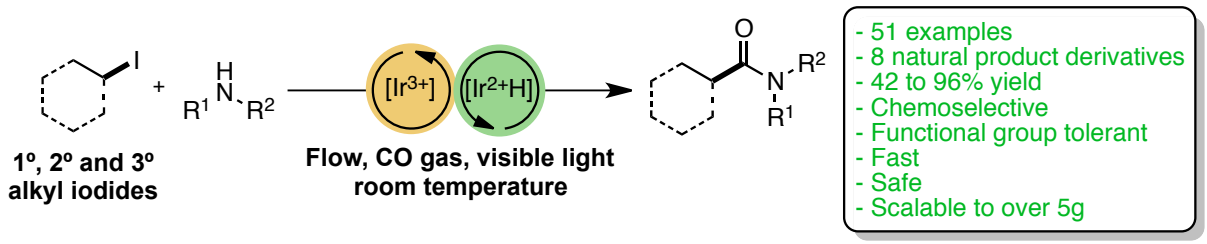
Here we report a method for the radical aminocarbonylation of unactivated 1°, 2° and 3° alkyl iodides using carbon monoxide as C1 building block. The process harnesses our recently discovered tandem photocatalytic cycle of the [Ir(dtbbpy)(ppy)$_2$]PF$_6$ photocatalyst[1] which engaged energy demanding alkyl iodides in combination with flow technology. The synthesis of 51 of alkyl amides is achieved in good to excellent yields and the method is applied to the late-stage functionalisation of a natural product. A bespoke flow chemistry platform was assembled from a HPLC pump, a gas liquid tube-in-tube reactor and blue LED photoreactor, enabling ambient pressures of CO, and short residence times. Mechanistic studies confirm the operation of a tandem photocatalytic cycle of the [Ir(dtbbpy)(ppy)$_2$]PF$_6$ complex and DFT calculations indicates that radical chain propagation has a crucial role in this reaction.



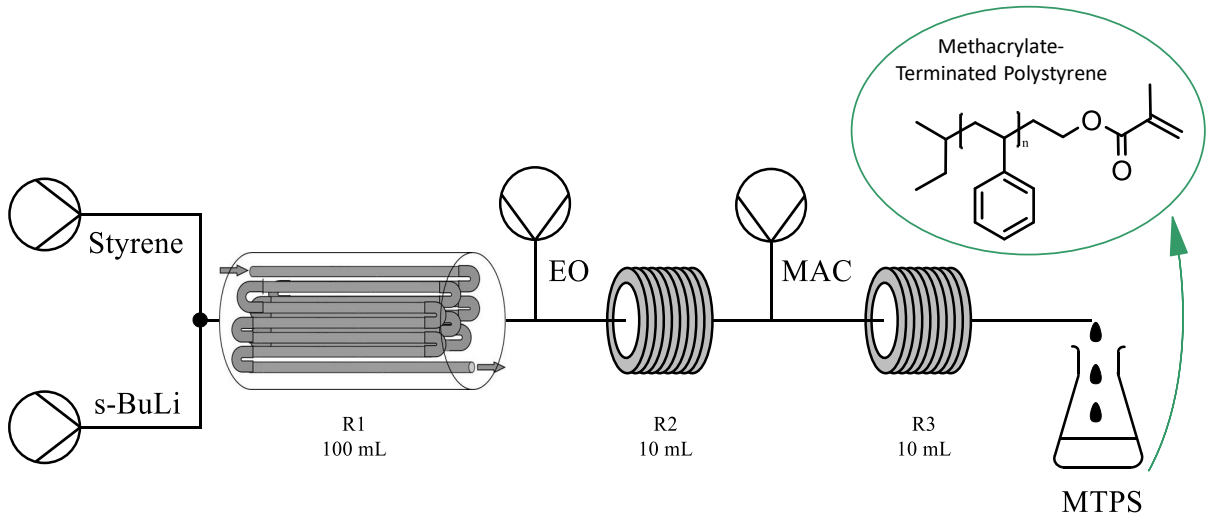
1. Connel, T. U.; Fraser, C. L.; Czyz, M. L.; Smith, Z. M.; Hayne, D. J.; Doeven, E. H.; Agugiaro, J.; Wilson, D. J. D.; Adcok, J. L.; Scully, A. D.; Gomez, D. E.; Barnett, N. W.; Polyzos, A.; Francis, P. S. *J. Am. Chem. Soc.* **2019**, *In Press*.

Autonomous Macromonomer Production with Flow Chemistry

Damian Fullston, Ivan Martinez-Botella, Nino Malic, Melissa Skidmore

CSIRO Manufacturing, Clayton VIC, Australia

Continuous flow chemistry was utilized for the autonomous manufacturing of methacrylate-terminated polystyrene (MTPS) macromonomers. Anionic polymerization of styrene was followed by ethylene oxide chain extension and subsequent methacryloyl chloride termination by sequential reagent addition along an integrated continuous flow path. Methacrylate-terminated polystyrene macromonomers of defined molecular weight were produced with greater than 99% styrene conversion and over 97% methacrylate end group functionality in under 20 minutes.



NANOMACHINE BIOCATALYSTS: TOOLS FOR CONTINUOUS FLOW BIOCATALYSIS

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Key Words: continuous flow biocatalysis, nanomachines, cofactor recycling.

Assembling cell-free, cascading multi-enzyme enzyme reactions continuous flow systems for the conversion of low value renewable feedstocks into high value products represents a fourth wave of biocatalysis for renewable green chemistry and synthetic biology applications [1]. However, major limitations to both applications include the cost of producing multiple purified enzymes and of providing a continuous supply of diffusible cofactors or cosubstrates [2]. We have applied synthetic biology principles to produce fusion proteins between enzymes and their cofactor-recycling partner enzymes, with concomitant *in situ* recycling of a modified tethered cofactor, with an added conjugation protein element to allow immobilization of the nanomachines to a surface. This has enabled the construction of nanomachine flow reactors which can be combined in an interchangeable, "plug-and-play" manner to construct complex synthetic continuous flow networks or Nanofactories [3]. Synthesis of the anti-diabetic drug, D-fagomine, reductive amination to produce various chiral or conjugated amines (Fig. 1) and deracemization of alcohols have been used to exemplify the principles, and we have demonstrated tethered cofactor recycling of ATP, $NAD(H)^+$ and $NADP(H)^+$, as well as ligand-directed immobilization of a variety of enzymes to illustrate the use of these nanomachine biocatalysts as tools for the *de novo* construction of continuous flow systems for synthetic biology and fine chemical synthesis. Our research is currently exploring the use of frugal innovation principles to integrate reactor design with on-line analytics for real-time reaction monitoring, and, subsequently, dynamic control over fluidics via feedback loops.

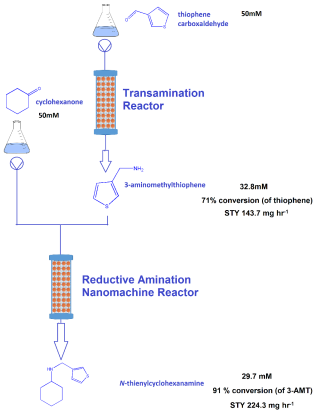

Figure 1: Continuous flow biocatalysis system combining transamination and reductive amination for the formation of conjugated amines.

[1] Bornschauer U.T. 2018. *Angew. Chem. Int*, *Ed.* 55: 4372-4373.

[2] Tamborini, L. *et al.* 2017. Flow bioreactors as complementary tools for biocatalytic process intensification. *Trend Biotechnol.* **36**, 73–88 (2017); Fessner W-D. 2015. New Biotechnology 32:658-664; Zhao et al., 2003. *Curr Opin Biotechnol* 14: 421-426.

[3] Hartley, C.J. et al. Engineered enzymes that retain and regenerate their cofactors enable continuous-flow biocatalysis. *Nature Catalysis* (2019).

The Application of Homogeneous and Heterogeneous Ring-Opening Polymerisation into Flow

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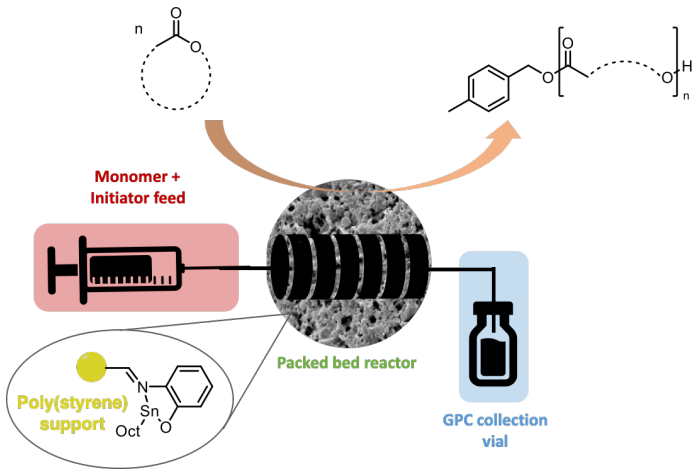
A significant amount of research has gone towards the development of sustainable alternatives to fossil fuel derived polymers; this has been driven in part by the increased awareness of the effect of plastics on the environment. Polymers from lactones such as *L*-lactide have received particular attention due to their biogenic properties. The use of heterogeneous catalysts in the production of these polymers has remained largely unexplored, despite significant study of homogeneous analogues. In fact, the former could offer both a means of producing polymers of high purity with low metal content without any extra purification. Further, the chance to recover and recycle the catalysts offers a significant economic benefit, and there is an added advantage of using the catalysts in a flow system to enable continuous polymer synthesis. Flow systems are well known for addressing many issues that plague batch processes; thereby improving mixing, heat transfer, and offering a viable way to scale up reactions. In particular, ring-opening polymerisation (ROP) of lactones in flow has previously been shown to produce polymers with excellent control over the dispersity and molecular weight (M_n).[1,2]

In this work, we present the development of heterogeneous metal complexes for use in the ROP of lactide, leading up to initial studies incorporating ROP into a flow set-up. A series of metal complexes were immobilised onto inert poly(styrene) (PS) supports and utilised in the ROP of various lactones in bulk conditions. **PS-L^{H}ZnOAc**, **PS-L^{H}SnOct** and **PS-L^{Cl}SnOct** were identified as the most successful heterogeneous catalysts for the ROP of *L*-lactide. Investigations by *in situ* ATR-FT-IR revealed conversions reaching *ca.* 90% in 55 minutes, with excellent molecular weight control and dispersities ($Đ_M$ 1.15–1.17). Catalyst reuse was also possible, with up to 7 reuse cycles, albeit accompanied by a progressive reduction in conversion. Due to the reusability of the catalysts, we are developing the application of these catalysts into flow systems, where the catalyst is immobilised into a packed bed, and continuous production of polymer is possible. Initial investigations of the homogeneous flow system also offer promising results, demonstrating the applicability of ROP into flow.



1 N. Zhu, W. Feng, X. Hu, Z. Zhang, Z. Fang, K. Zhang, Z. Li and K. Guo, Polymer, 2016, 84, 391–397.
2 B. Lin, J. L. Hedrick, N. H. Park and R. M. Waymouth, J. Am. Chem. Soc., 2019, 141, 8921–8927.

Organocatalytic Decarboxylation of Amino Acids in Continuous Flow: A Scalable Route to 3-Hydroxypyrrolidine

Rowan Pilkington[1], Paul Savage[1] and Anastasios Polyzos[1,2]

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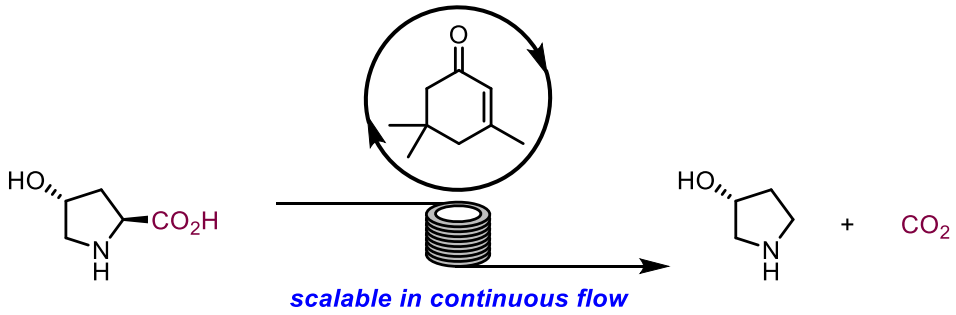
2. School of Chemistry, The University of Melbourne, Parkville, VIC 3010, Australia

The decarboxylation of amino acids represents a straightforward route to the production of versatile amines from inexpensive and abundant bio-feedstock. In the presence of an enone organocatalyst, the thermal decarboxylation of α–amino acids readily occurs at high temperatures. However, this reaction must be performed under pressurised 'bomb' conditions or under microwave irradiation, preventing effective transferal to scales beyond the laboratory bench.

For the first time, homogenous continuous flow methods enable the rapid, high-throughput decarboxylation of α-amino acids. The process is mediated by an inexpensive and recyclable enone, yielding product amines in high purity after aqueous extraction. This methodology has been applied to the preparation of valuable (*R*)-3-hydroxypyrrolidine from *trans*-4-hydroxyproline.



Multistep Synthesis of Benzhydrylamines via Photoredox Catalysed Transfer Hydrogenation in Continuous Flow

Edward Phung[a], Anastasios Polyzos[a,b]

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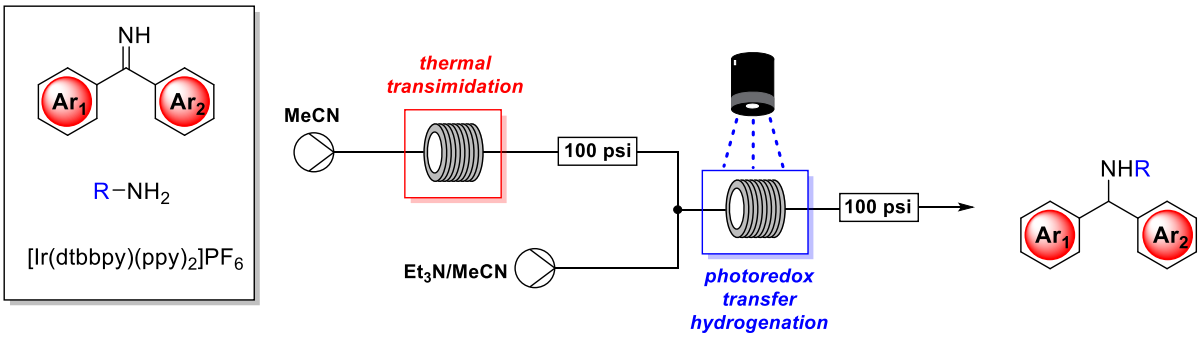
[b] *CSIRO Manufacturing, Clayton South, VIC*

The multistep synthesis of biologically relevant benzyhdrylamines has been demonstrated combining principles of flow chemistry and photoredox catalysis. The synthesis was conducted using commercially available reagents via thermal transimination to afford N-substituted imines. Using Et_3N as both a single electron donor and hydrogen atom donor, the transfer hydrogenation of the diarylimines in the presence of the photocatalyst $[Ir(dtbbpy)(ppy)_2]PF_6$ was readily achieved. The reaction scope of this multistep flow process is broad and we demonstrate the practicality of this method through facile scale-up and synthesis of an active pharmaceutical ingredient.



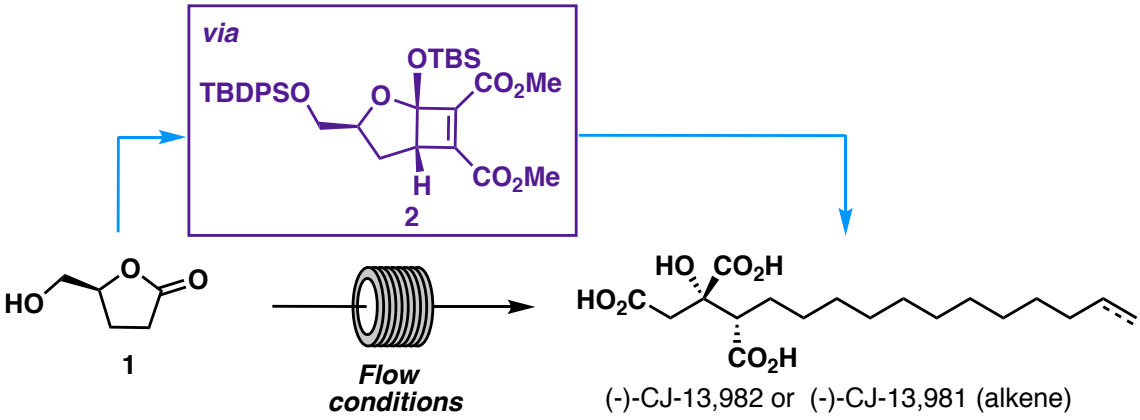
Towards the Continuous Flow Synthesis of Alkyl Citrate Natural Products

Nikolai Piers Rossouw,[1] Mark A. Rizzacasa[1] and Anastasios Polyzos[1,2]

[1]*School of Chemistry, The University of Melbourne, Parkville, VIC*

[2]*CSIRO Manufacturing, Clayton South, VIC*

The alkyl citrate family of complex fungal metabolites are potent inhibitors of squalene synthase (SSase), a key enzyme implicated in the biosynthesis of cholesterol. This presentation will detail our efforts toward the continuous flow total synthesis of citrates (-)-CJ-13982 and (-)-CJ-13981 via the cyclobutene diester **2**, from biomass derived (*S*)-(+)-γ-hydroxymethyl-γ-butyrolactone **1**.



Absolute control over molecular weight distributions through autonomous polymer synthesis

Maarten Rubens[1,2], *Jeroen Vrijsen*[2], *Joachim Laun*[2], *Tanja Junkers*[1,2]

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Fully self-optimizing autonomous reactors for organic synthesis have emerged in the last few years. The role of automation in chemical synthesis can be categorized into three distinct categories; *autonomous high throughput screening, autonomous optimization* and *enhanced process control.* A typical autonomous reactor consists out of an external controlled continuous flow reactor platform coupled with spectroscopy based online analysis tools. The online analysis tools provide direct information on the progress of the reaction and permits for a direct steering to the intended reaction trajectory. While these reactors are well developed in the field of organic transformation, no such system exists for polymer synthesis yet.

In our research we designed successfully an autonomous platform for polymerization reactions whereby a conventionally calibrated online SEC system is coupled to an external controlled continuous flow reactor platform. A generic algorithm was designed to optimize the average molecular weight to a predefined target under optimal conditions (low dispersities and high monomer conversion).[1] In short, the automated synthesis platform is able to target series of average molecular weights of (meth)acrylate polymers with an accuracy of less than 2.5 % while requiring no human interaction beyond the start-up phase. The developed technology is used to synthesize artificial molecular weight distributions by precisely combining multiple discrete polymer samples with targeted molecular weight. This way the autonomous polymerization setup is able to control and tune both the molecular weight and dispersity of the final polymer sample.[2]

The automated flow platform is a first step in synthesizing systematic polymer libraries with unprecedented control over the materials properties in a reproducible fashion. Such accessible tailor-made libraries, both in molecular weight and dispersity, are anticipated to have an impact in the domains of self-assembly, drug-delivery, and materials design.

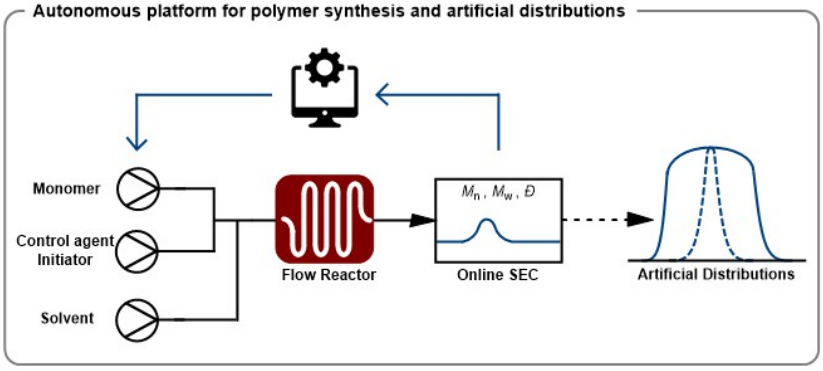

Figure 1. Schematic overview of experimental setup. The product stream is injected into an online SEC system and subsequently analysed and processed by the optimization algorithm.

[1] M. Rubens, J. Vrijsen, J. Laun, T. Junkers, *Angew. Chem. Int. Ed*. **2019,** 58, 3183-3187
[2] M. Rubens, T. Junkers, *Polymer Chemistry* **2019**, Advance Article

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The Visible Light Mediated Radical Decarboxylative α-Alkylation of Amines in Continuous Flow

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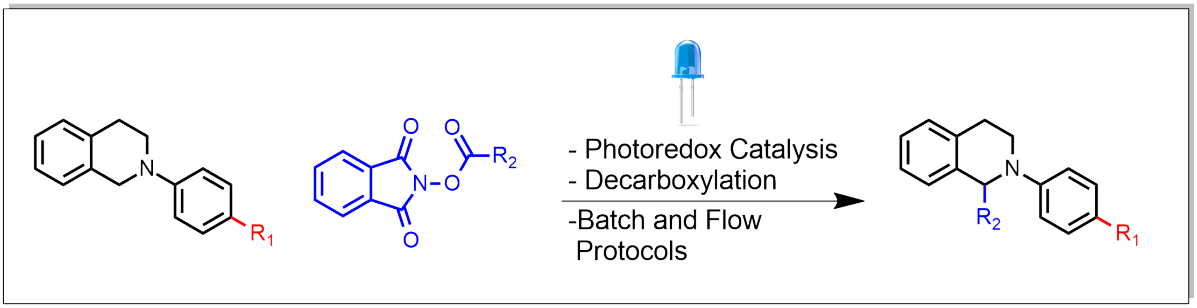
Fused bicyclic amines are an important structural motif due to their presence in a variety of pharmaceuticals and natural products. Thus, there is an ongoing demand for improvement in the synthesis and functionalization surrounding fused bicyclic amines. Photoredox chemistry has stimulated a renaissance in radical based methodology[1], with the visible light mediated α-functionalization of amines having been reported previously[2]; however, the methodology is typically limited to nucleophilic addition of the iminium ion[3] or radical addition to a Michael acceptor[4].

This work presents the α-alkylation of one class of fused bicyclic amines, the tetrahydroisoquinolines (THIQ), via a visible-light mediated radical-radical coupling process. N-Hydroxyphthalimide (NHP) esters derived from commercially available carboxylic acids were employed as an alkyl radical source to undergo coupling with α-amino radicals generated via photocatalytic methods. The development of a flow protocol is reported.



[1] Prier, K. C., Rankic, D. A., MacMillan D. W.C. *Chem Rev.* **2013**,113, 5322
[2] Hu, J., Wang, J., Nguyen, T., Zheng, N. *Beilstein J. Org. Chem.* **2013**, 9, 1977.
[3] Condie, A. G., González-Gómez, J. C., Stephenson, C. R. J. *J. Am. Chem. Soc.* **2010**, 132, 14644
[4] Kohls, P., Jadhav, D., Pandey, G., Reiser, O. *Org. Lett.*,. **2012**, 14, 672

Automated Polymer Synthesis Platform for Integrated Conversion Targeting Based on Inline Benchtop NMR

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The implementation of analytical devices inline into the synthesis stream allows close monitoring of chemical reactions. Flow chemistry can benefit especially from in- and online analysis as flow rates can be adapted dynamically, allowing for precise reaction control. By adding self-optimizing feedback loops and machine learning principles to the process, a precision and accuracy can be obtained that is hard or even impossible to achieve by human experience and intuition. Batch polymerisations are known to be prone to batch-to-batch variations and their offline analyses are often time-consuming. The combination of flow chemistry, online/inline monitoring and computer-guided software resolves these issues and leads to an increased reproducibility and efficiency in polymer synthesis. A benchtop NMR spectrometer was coupled to the outlet of a flow reactor for inline analysis of monomer conversion during control radical polymerizations.[1] Timesweep experiments – these are experiments in which residence times are screened rapidly in a single experiment – were performed in order to acquire the whole kinetic profile of thermal RAFT polymerisations in less than one hour. Additionally, an algorithm was programmed that allows targeting pre-defined monomer conversion by choosing the appropriate residence time independently and adjusting the flowrate accordingly. Offline analysis of the synthetised polymer samples reveals a high accuracy and precision in molecular weight distributions with deviations of only 3%. As an upgrade of the platform, also the synergistic coupling of inline NMR and online gel permeation chromatography will be discussed.

(1) Rubens, M.; Van Herck, J.; Junkers, T. Automated Polymer Synthesis Platform for Integrated Conversion Targeting Based on Inline Benchtop NMR. *ACS Macro Lett.* **2019**, 1437–1441. https://doi.org/10.1021/acsmacrolett.9b00767.

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Geethi Weragoda

A clean and green photochemical protocol for the di- & tri-fluoromethylation of heteroarenes

The selective incorporation of fluorinated motifs, in particular CF_3 and CF_2H groups, into organic compounds has emerged increasing attention since organofluorine molecules are of the utmost importance in the areas of pharmaceutical, agrochemical, and material sciences. Herein we successfully report the use of CH_2FSO_2Na and CH_3SO_2Na reagents as the fluorinating source in batch and continues flow. A simple, green and transition-metal-free protocol has been applied in challenging di- and tri-fluoromethylation of electron-rich heteroarenes. Additionally, this protocol is distinguished by utilising readily available, cheap reagent diacetyl as the blue light absorber and solvent sensitizer which initiate the single electron transfer processes. Generality of this reaction was demonstrated with the substrates that are important building blocks for pharmaceuticals such as indoles, pyrroles and pyrazines.

Nanomachine Biocatalysts: multi-enzyme cascades for sustainable industrial chemistry

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Continuous flow chemistry offers many advantages over traditional batch reactions, including, reaction flexibility due to the modular nature of flow reactors, improved scalability and yield, facile isolation of the product and greater safety. Biocatalysis offers complementary advantages, particularly with respect to high regio- and stereo-specificity. Continuous flow-reactors containing immobilized enzymes may offer many of the same advantages of modularity, scalability and yield and provide exquisite regio- and stereo-selectivity: however, for enzymes requiring cofactors the cost of continuously supplying cofactor can be prohibitive. When recycling cofactors in a flow system, the enzyme, the cofactor recycling enzyme and the cofactor must all be immobilized in such a way that the cofactor is free to participate in reactions with both enzymes. We have produced engineered enzymes that retain and recycle their cofactors, and can be immobilised to a surface, which enable their use in continuous flow reactors. Multiple enzyme-based continuous flow reactors can be connected in a modular fashion to achieve multistep transformations.

We set out to produce fusion proteins between synthetic enzymes and their cofactor-recycling partner enzymes with concomitant *in situ* recycling of a modified tethered cofactor, thus combining the advantages of biocatalysis and *in situ* cofactor-recycling. We have developed fit-for-purpose multi-enzyme fusion proteins with tethered cofactors to catalyse these reactions, with each fusion protein comprising a synthetic domain and a cofactor-recycling domain (**Fig. 1a**).

Furthermore, we have produced a prototype reactor, based on our modular design, to synthesise the anti-diabetic drug D-fagomine. With three stereocentres the chemical synthesis of D-fagomine is complex, we have shown it can be produced enzymatically in a flow reactor from glycerol *via* two regiospecific, cofactor-dependent steps (an ATP-dependent phosphorylation and an NAD-dependent oxidation) and a stereospecific aldol condensation to produce the precursor to D-fagomine (3*S*,4*R*-dihydroxyketone), the final chemical step requires simultaneous deprotection and reductive cyclisation (**Fig. 1b**).

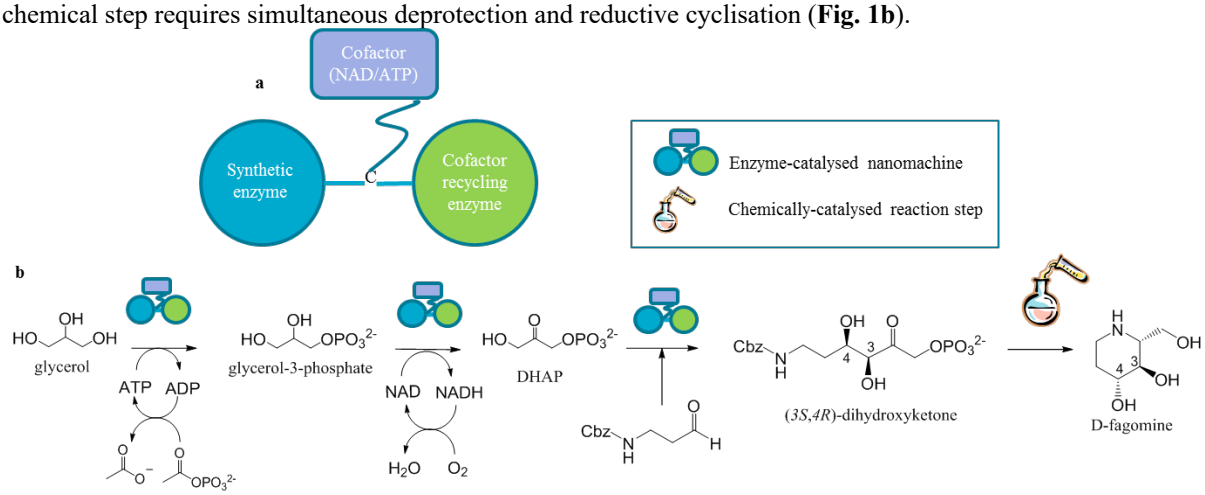

Figure 1: a) Bi-enzymatic fusion protein with tethered cofactor; **b)** Multi-enzyme cascade demonstrating synthesis of D-fagomine