

## Flow Chemistry at a glance

**Continuous flow processing has been amongst the most significant step changes in API synthesis at scale for the past decade. In Ireland, the ecosystem spans internationally leading research teams at the universities, providing the next generation of early career researchers to drive this activity, through to leading multinational pharmaceutical manufacture at scale, as well as CDMOs. SSPC plays a key role in ensuring the efficiency of the exchange of ideas, expertise and people at the industry-academic interface to ensure the Irish pharma sector has the skills needed to continue to grow and develop as a leader in utilising continuous flow technology in the GMP manufacture of APIs.**

Editorial: Prof. Anita R Maguire and Dr Marcus Baumann

### Continuous Flow Photochemistry

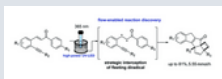


Dr Marcus Baumann



Continuous flow is advantageous for photochemical reactions due to high photon transfer rates and uniform irradiation with good scalability for many important transformations. The Baumann group at UCD has exploited these features using commercially available reactors to affect the scaled synthesis of C-C bonds via TBADT-catalysed HAT processes, the preparation of various cyclobutene products, the generation of oxazole and quinoline-based scaffolds via reagent-free means as well as various innovative skeletal rearrangements to generate complex carbocyclic scaffolds as well as ketenimine building blocks that allow for the expedited generation of medicinally relevant chemical entities. Recent work with the Maguire group showcased the application of diazo compounds in continuous photochemical C-H insertion processes.

#### Publication



Di Filippo, M| Trujillo, C| Sánchez-Sanz, G. |Batsanov, AS | **Baumann, M., Discovery of a Photochemical Cascade Process by Flow-based Interception of Isomerising Alkenes, *Chem. Sci.* 2021, 12, 9895.**

### Diazo Chemistry in Flow



Prof. Anita R. Maguire,  
Dr Stuart Collins

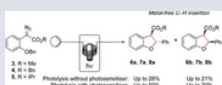


Katie O'Callaghan, PhD



Flow processing offers considerable advantages in the safe generation and use of hazardous reagents. While the synthetic versatility of  $\alpha$ -diazocarbonyl compounds is very clear, resulting in a wide range of transformations which cannot be readily effected through other methodologies, safety concerns limit their use in large scale API synthesis. Research from the Maguire-Collins team has shown that  $\alpha$ -diazocarbonyl compounds can be safely generated and used in continuous flow, thereby overcoming some of the barriers to their use at scale. Use of in line reaction monitoring (FlowNMR and FlowIR through the **(ABCRF ProSpect facility)** offers clear advantages in terms of process safety and control. Perhaps the most important outcome of this work is the demonstration that enantioselective transition metal catalysis can be successfully telescoped downstream of the generation of sulfonyl azides and diazo transfer steps without negatively impacting on the enantioselectivity of the metal catalysts, despite the complexity of the reaction streams, which could potentially interfere with the sensitive catalysts.

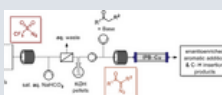
#### Publications



O'Callaghan, K.S.| Lynch, D.| **Baumann, M.**| Collins, S.G.| Maguire, AR., **Flow photolysis of aryldiazoacetates leading to dihydrobenzofurans via intramolecular C-H insertion *Org. Biomol. Chem.*, 2023, 21, 4770-4780**



Kearney, AM| Lynch, D. | **Collins, SG |Maguire, AR., Telescoped diazo transfer and rhodium-catalysed S-H insertion in continuous flow. *Tetrahedron Lett*, Volume 83,, 2021, 153438**



Crowley, DC| Kearney, AM| Lynch, D. |Ford, A. | **Collins, SG |Maguire, AR., Exploiting Continuous Processing for Challenging Diazo Transfer and Telescoped Copper-Catalyzed Asymmetric Transformations. *J. Org. Chem*, Volume 86, Issue 20, 2021, 13955-13982.**

# Telescoping High-Energy Curtius Rearrangements with Flow Biocatalysis



Dr Marcus Baumann



High-energy species such as azides are frequently exploited in safe flow transformations such as the Curtius rearrangement to convert carboxylic acids into amines. In a recent collaboration between the Baumann group and Almac Sciences, a telescoped flow process showcasing the DPPA-mediated Curtius rearrangement and subsequent trapping of the reactive isocyanate intermediate with benzyl alcohol was demonstrated. Crucially, a biocatalysed downstream derivatisation method was incorporated to convert high-boiling benzyl alcohol into easily removable benzyl ester was used exploiting an immobilised CALB enzyme. This telescoped method tolerated the spent reagent and could be scaled to prepare decagram quantities of the resulting Cbz-carbamate products that could be isolated in clean form after simple trituration thus obviating the challenges associated with using the high-boiling benzyl alcohol in excess.

## Publication



Baumann, M. | Leslie, A. | Moody, TS | Smyth, M. | Wharry, S., Tandem Continuous Flow Curtius Rearrangement and Subsequent Enzyme-Mediated Impurity Tagging, *Organic Process Research & Development*, 2021, Volume 25, Issue 3, 452

# Design, Optimisation and Scale-up of Continuous Reactors



Prof. Vivek Ranade  
Dr Amol Ganjare, Postdoc



Dr Rob Elmes  
Dr Stephen Healy, Postdoc



The rates of transport processes in conventional batch reactors and intensified continuous reactors differ by order(s) of magnitude and therefore complex interactions between intrinsic reaction kinetics, rates of transport processes and the reactor performance change dramatically as one moves from batch to continuous reactors.

The objective of this industry collaboration is to develop appropriate models for interpreting batch and continuous experiments as well as for designing, optimising and scaling-up of continuous reactors. In this project, the methodology will be developed, tested and validated for a suite of case studies on neutralisation of acidic waste streams from manufacturing facilities.

## Publication



Dongaonkar, P. | Mummudi, M. | Kasat, D. | Vedapuri, G. | Ranade, V., Digitalize Process Assets for Improving Productivity: Enhance Process Insights, Metric, and Parameters via Simulations; *Handbook of Multiphase Flow Science and Technology*, G. H. Yeoh (ed.), Springer Nature Singapore Pte Ltd. 2022

# Selected Publications From SSPC Flow Investigators



Dr Ger McGlacken



Cooper, E., | Alcock, E. | Power, M. | McGlacken, G.P., The  $\alpha$ -alkylation of Ketones in Flow *React. Chem. Eng.*, 2023, 8, 1839. (Paper highlighted in OPR&D July 2023).

The McGlacken group are focused on the use of flow technology to avoid cryogenic conditions and troublesome side products. A particular focus is the use of organometallics in flow.



Fitzgerald, S. | O'Shea, D.F. Continuous Flow Bioconjugations of NIR-AZA Fluorophores via Strained Alkyne Cycloadditions with Intra-Chip Fluorogenic Monitoring *Chemistry A European Journal* Volume 28, Issue 11, February 21, 2022



Srinivasan, S. | Van den Akker, H.E.A. | Shardt, O. Shear thickening and history-dependent rheology of monodisperse suspensions with finite inertia via an immersed boundary lattice Boltzmann method *International Journal of Multiphase flow* Volume 125, April 2020, 103205



Harding, M.J. | Feng, B. | Lopez-Rodriguez, R. | O'Connor, H. | Dowling, D. | Gibson, G. | Girard, K.P. | Ferguson, S. Concentric annular liquid-liquid phase separation for flow chemistry and continuous processing *React. Chem. Eng.*, 2021, 6, 1635-1643

# SSPC Flow Capabilities

## Photochemistry



Dr Marcus Baumann, UCD  
Prof. Anita Maguire, UCC  
Dr Stuart Collins, UCC

## Organic Synthesis



Prof. Anita R. Maguire, UCC  
Prof. Edmond Magner, UL  
Dr Stuart Collins, UCC  
Dr Ger McGlacken, UCC  
Prof. Paul Murphy, University of Galway  
Dr Humphrey Moynihan, UCC

## Biologics in Flow



Prof. Donal O'Shea, RCSI  
Prof. Marc Devocelle, RCSI  
Dr Rob Elmes, MU  
Dr Eoin Scanlon, TCD  
Dr Ioscani Jimenez Del Val, UCD

## Flow, Mixing, Reactions & Process Intensification



Prof. Harry Van den Akker, UL  
Dr Steven Ferguson, UCD  
Prof. Pat Frawley, UL  
Prof. Gavin Walker, UL  
Prof. Vivek Ranade, UL  
Dr Kevin Moroney, UL  
Dr Michael Vynnycky, UL  
Dr Orest Shardt, UL



For more information on SSPC and the SSPC Flow Community of Practice, please contact SSPC Industry Engagement Manager [aisling.arthur@ul.ie](mailto:aisling.arthur@ul.ie)