

Welcome to the **Flow Synthesis Online** newsletter.

This publication is released generally bi-monthly (major holiday periods permitting) and will showcase new applications, events, and equipment in the Flow Synthesis world.

It's interesting how certain topics come in "waves". Last issue we had two separate ozonolysis stories. In this issue, two different publications report on the use of ultrasound to enhance reaction outcomes in some way.

In this issue

Applications - *Dealing with organometallic reagents*

Product News - *New Cooled column reactor*

Events - *Where and when to see Vapourtec systems in action*

Publications - *New flow chemistry publications from the last few weeks*

Enjoy.

Vapourtec sent this email to you because you have in the past expressed an interest in Vapourtec products. If you do not want to receive future issues of this newsletter, you may unsubscribe now by scrolling to the bottom of this email and clicking on the unsubscribe link. If you think a colleague may be interested, please feel free to forward it.

Applications

How to handle Organometallic Reagents

Organometallic reagents can present a challenge to the flow chemist, reacting readily with moisture or air that they come into contact with, and generating hard insoluble precipitates inside pumps and valves.

But with the right approach, it is possible to handle these reagents in a stable and reliable fashion.

[Click here to find out more](#)

Product News

Cooled Column Reactor now available

Earlier in the year Vapourtec launched a cooled tube reactor for homogeneous reactions down to -70°C.

Now the cooled *column* reactor is here !

Heterogeneous reactions can now be cooled to -40°C, with no need for a recirculating chiller.

[Click here for more details](#)



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Is it your first time ?

If this is the first issue of the newsletter that you've received, you might like to take a look at what you've missed in some previous issues.

[click here to see newsletter archive](#)

Events

Attendees of the following events will be able to see the latest Vapourtec Flow Chemistry equipment in action, and no doubt talk to other users.

1st RSC/SCI Symposium on Continuous Processing and Flow Chemistry

3-4 November, GlaxoSmithKline Stevenage, Herts, UK

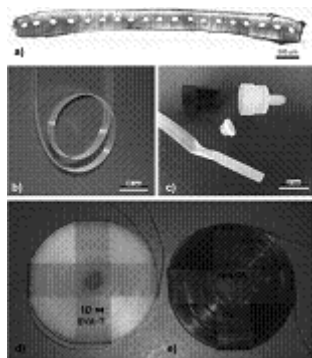
[Herts, UK Click here for full details of this event.](#)

UK Automated Synthesis Forum (UKASF)

17-18 November, Novartis, Horsham, UK

Publications

A Palladium Wall Coated Microcapillary Reactor for Use in Continuous Flow Transfer Hydrogenation



C.H. Hornung¹, B. Hallmark¹, M.R. Mackley¹
I.R. Baxendale² and S.V. Ley²

¹ Dept of Chem Eng, Univ of Cambridge

² Innovative Technology Centre, Dept of Chemistry, Univ. of Cambridge

A novel continuous flow multi-channel microreactor in which the internal surface has been functionalised with a palladium coating, enabling its use in catalytic heterogeneous liquid-phase reactions. The functional activity of the catalytic Pd layer was tested in a series of transfer hydrogenation reactions using triethylsilane as the hydrogen source.

[Click here to go straight to the publication](#)

A Gram-Scale Batch and Flow Total Synthesis of Perhydrohistrionicotoxin

Dr. Malte Brasholz¹, Dr. James M. Macdonald¹, Dr. Simon Saubern¹, Dr. John H. Ryan¹, Prof. Dr. Andrew B. Holmes^{1,2}

¹CSIRO, Melbourne, Australia

²Bio21 Institute, University of Melbourne, Australia

Biologically valuable histrionicotoxin spiropiperidine alkaloids are found in the Colombian poison arrow frog *Dendrobates histrionicus* shown in the illustration.

The total synthesis of the spiropiperidine alkaloid (–)-perhydrohistrionicotoxin (perhydro-HTX) has been accomplished on a gram scale by employing both conventional batch chemistry as well as microreactor techniques.

[Click here to go directly to the publication](#)



KMnO₄-Mediated Oxidation as a Continuous Flow Process

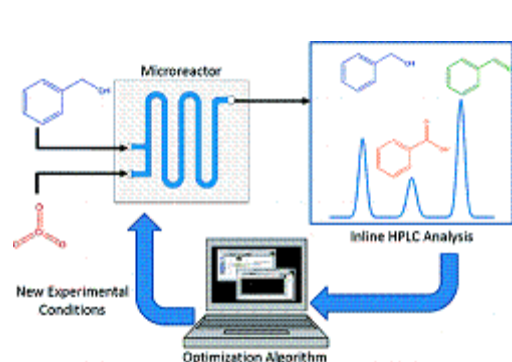


Jorg Sedelmeier, Steven V. Ley, Ian R. Baxendale and Marcus Baumann

Innovative Technology Centre, Department of Chemistry, University of Cambridge

An efficient and easily scalable transformation of alcohols and aldehydes to carboxylic acids and nitroalkane derivatives to the corresponding carbonyls and carboxylic acids using permanganate as the oxidant within a continuous flow reactor is reported. Notably, the generation and downstream processing of MnO_2 slurries was not found to cause any blocking of the reactor when ultrasound pulses were applied to the flow system.

[Click here to go straight to the publication](#)



An Automated Microfluidic System for Online Optimization in Chemical Synthesis

Jonathan P. McMullen and Klavs F. Jensen

Dept of Chemical Engineering, Novartis-MIT Center for Continuous Manufacturing, Cambridge, U.S.A.

An automated, continuous flow system for the online, multivariable optimization of a chemical reaction is presented. Time and material required for an optimization trial are minimized by performing reactions in an integrated

silicon microreactor and incorporating an HPLC for inline monitoring of the reaction performance. We use the system to optimize two different reactions to describe the potential impact of this system for reaction development. First, we demonstrate the broad operation capabilities by incorporating several feedback algorithms to optimize a weighted objective function involving the yield and the throughput of a Knoevenagel condensation reaction. After illustrating how system operations can be adapted for individual reactions, we perform a multiparameter optimization to maximize the yield of benzaldehyde in the oxidation pathway of benzyl alcohol to benzaldehyde to benzoic acid. A significant feature of the automated system is the ability to perform "black-box" optimization where no a priori information of the reaction parameters is required.

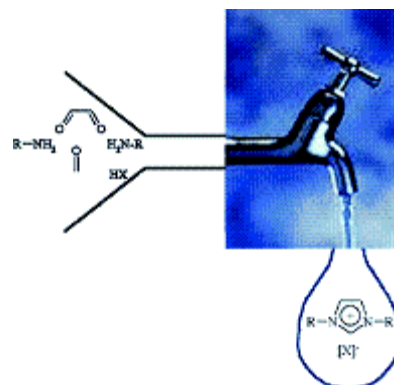
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Efficient Synthesis of 1,3-Dialkylimidazolium-Based Ionic Liquids: The Modified Continuous Radziszewski Reaction in a Microreactor Setup

Johannes Zimmermann, Bernd Ondruschka, and Annegret Stark

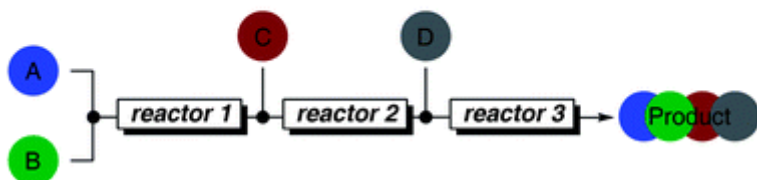
*Institute for Technical Chemistry and Environmental Chemistry,
Friedrich-Schiller University, Jena, Germany*

By making use of a modified Radziszewski reaction, it is demonstrated that water-soluble 1,3-dialkylimidazolium-based ionic liquids can be produced in good yields (70–90%) and purities (>95%) starting from readily available, cost-effective monoalkylamines, glyoxal, formaldehyde, and mineral or organic acids. The homosubstituted 1,3-dialkylimidazolium salts feature high thermal stabilities similar to those of their heterosubstituted counterparts, and relatively low viscosities, thus fulfilling the requirements for solvent application. The effect of various parameters has been studied with the goal of improving yields for both the batchwise and continuous synthesis (making use of a microreactor setup), allowing for the production of a wide variety of ionic liquids and the introduction of functionalities. The applicability of these ionic liquids is demonstrated on the example of cellulose dissolution and the dehydration of fructose to 5-hydroxymethylfurfural.



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Continuous Flow Multi-Step Synthesis Sequential Reactions in a Multi-Reactor Network



single continuous operation.

Continuous flow multi-step organic synthesis (Review)

Damien Webb and Timothy F. Jamison

*Novartis-MIT Center for Continuous
Manufacturing, Cambridge, USA*

Using continuous flow techniques for multi-step synthesis enables multiple reaction steps to be combined into a

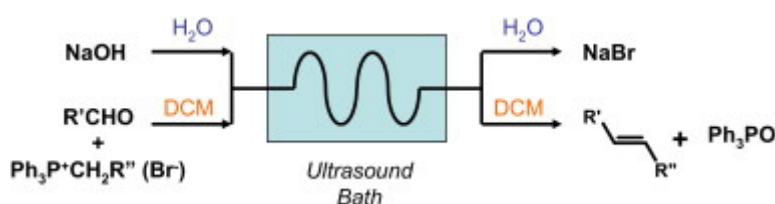
In this mini-review we discuss the current state of the art in this field and highlight recent progress and current challenges facing this emerging area.

[Click here to go straight to the publication](#)

Effect of phase transfer chemistry, segmented fluid flow, and sonication on the synthesis of cinnamic esters

Mauro Riccaboni, Elena La Porta, Andrea Martorana, Roberta Attanasio

*Department of Medicinal Chemistry,
NiKem Research Srl, Milan, Italy*



Wittig reaction under Phase Transfer conditions was performed in a flow reaction system. Different bases, aldehydes, phosphonium salts, and flow reaction parameters were investigated, in absence of a phase transfer catalyst. An improvement of the reaction outcome (yield and reaction time) was achieved through the immersion of the reactor into an ultrasound bath.

[Click here to go straight to the publication](#)

The technical articles above are in PDF form and may be immediately downloaded or read online. No registration is required. Enjoy !

Any 3rd Party publications referred to may require a subscription to download.

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