

Welcome to the March 2011 issue of the Flow Synthesis Online newsletter.

Lots of interesting stuff.

- 3 new product announcements including **UV Triggered Collection of Product peaks**
- A new "Case Study" feature
- A chance to get half price registration for the Flow Chemistry Congress in Boston
- Lots of new flow publications ranging from azide chemistry through magnetic mixing to RAFT polymerization.

We appreciate all your feedback so please keep it coming.

You have received this email because you have in the past expressed an interest in Vapourtec Flow Chemistry products. If you'd prefer not to receive this newsletter any more, use the unsubscribe link at the end of the email.

Product Announcements

UV Triggered Product Collection

Though Vapourtec's FlowCommander software can predict the start and end of reaction product peaks in most situations, there are some situations when it cannot give the full picture.

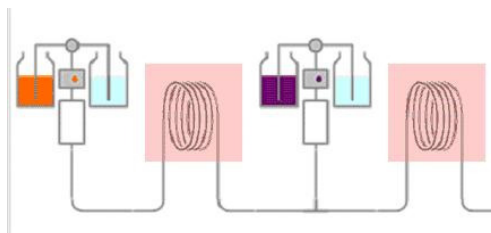
So, in response to requests from several users, it is now possible to automatically collect product peaks based on the output of a UV sensor.



[Click here for more details](#)

Flow Commander Update

New features have been added to Flow Commander to make it even quicker and easier to configure pump and reactor layouts.



[Click here for more details](#)

Larger Volume Reactors

The Vapourtec R Series permits 4 reactors to be used in series. With 10 ml reactors, this means a maximum effective reactor size of 40ml. But for some reactions with long residence time, even a 40 ml reactor may not be enough.

So a new style reactor coil of 25ml capacity has been developed, for a possible

total effective reaction volume of 100ml.

[Click here for more details](#)

Announcements

Vapourtec Asia office now open.

The new office in Kuala Lumpur is open for business.

[Click here for full contact details](#)

Events

Flow Chemistry Congress - Boston 28/29 April

Vapourtec will be attending this event (and exhibiting the latest options for the R Series flow chemistry system).

If you're planning to be there as an industry delegate, you can get **half price registration** with a special deal negotiated by Vapourtec.

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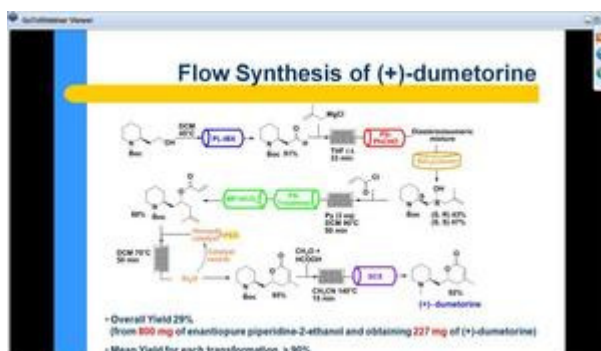
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Case Study

Nikem Research

In a new newsletter feature, we take a look at a company who have adopted and exploited continuous flow chemistry.



In this issue - NiKem Research, of Milan.

Formed in 2001 from GSK's Milan Research Group, NiKem have been into continuous flow chemistry since 2007.

They recently broadcast a webinar showing the work they have been doing in flow. The webinar was recorded and can now be downloaded.

[See the case study and a replay of the webinar](#)

Publications

Decarboxylative biaryl synthesis in a continuous flow reactor

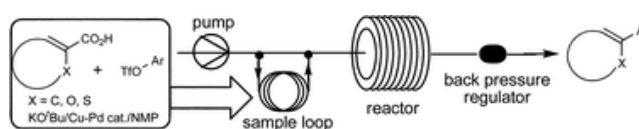
¹Paul P. Lange

¹Lukas J. Goößen

²Philip Podmore

²Toby Underwood

²Nunzio Sciammetta



¹Technische Universität Kaiserslautern, Germany

²Pfizer Global R&D, Sandwich, UK

A practical protocol was developed that allows performing decarboxylative cross-coupling reactions in continuous flow reactors. Various biaryls were thus synthesized from aromatic carboxylic acids and aryl triflates using a Cu/Pd-catalyst system.

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

Diastereoselective Chain-Elongation Reactions Using Microreactors for Applications in Complex Molecule Assembly

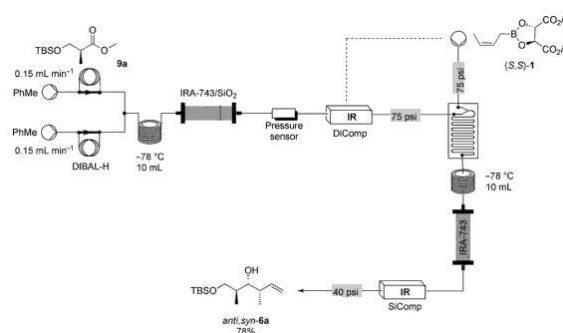
Catherine F. Carter¹

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Diastereoselective chain-elongation reactions are important transformations for the assembly of complex molecular structures, such as those present in polyketide natural products. Here we report new methods for performing

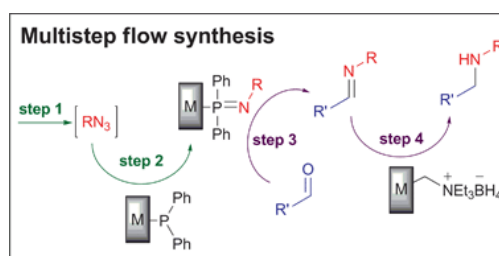
crotylation reactions and homopropargylation reactions by using newly developed lowtemperature flow-chemistry technology. In-line purification protocols are described, as well as the application of the crotylation protocol in an automated multi-step sequence.

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

Flow synthesis of organic azides and the multistep synthesis of imines and amines using a new monolithic triphenylphosphine reagent

Catherine J. Smith
Christopher D. Smith
Nikzad Nikbin
Steven V. Ley
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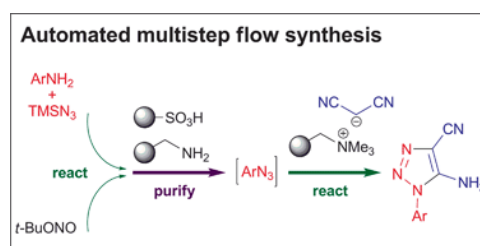


Here we describe general flow processes for the synthesis of alkyl and aryl azides, and the development of a new monolithic triphenylphosphine reagent, which provides a convenient format for the use of this versatile reagent in flow. The utility of these new tools was demonstrated by their application to a flow Staudinger aza-Wittig reaction sequence. Finally, a multistep aza-Wittig, reduction and purification flow process was designed, allowing access to amine products in an automated fashion.

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

A fully automated, multistep flow synthesis of 5-amino-4-cyano-1,2,3-triazoles

Catherine J. Smith
Nikzad Nikbin
Steven V. Ley
Heiko Lange
Ian R. Baxendale
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Having demonstrated in the preceding publication the flow synthesis of aryl azides, we describe here a general protocol for the in-line purification of these versatile intermediates. As part of this investigation, we evaluated the use of ReactIR 45m as a tool for real-time detection of hazardous azide contaminants. This azide synthesis and purification process was then incorporated into a multistep flow sequence to generate a small collection of 5-amino-4-cyano-1,2,3-triazoles directly from aniline starting materials in a fully automated fashion.

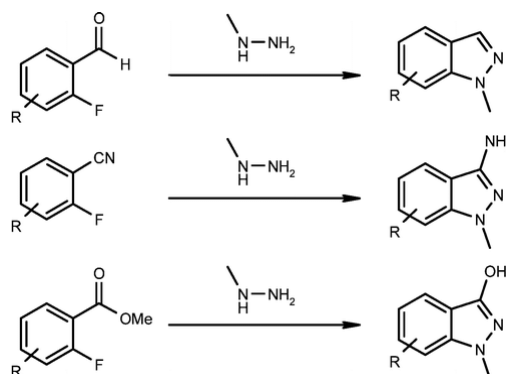
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A General, One-Step Synthesis of Substituted Indazoles using a Flow Reactor

Rob C. Wheeler
Emma Baxter
Ian B. Campbell
Simon J. F. Macdonald

GlaxoSmithKline, Stevenage, UK

The advantages of flow chemistry, increased safety, improved reproducibility, enhanced scalability, are readily apparent, and we aimed to exploit this technology in order to provide small amounts of pharmaceutically interesting fragments via a safe and scalable route, which would enable the rapid synthesis of multigram quantities on demand. Here we report a general and versatile route which utilises flow chemistry to deliver a range of known and novel indazoles, including 3-amino and 3-hydroxy analogues.



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Continuous flow synthesis of fullerene derivatives

Helga Seyler
Wallace Wing Ho Wong
Dave Jones
Andrew B. Holmes

University Of Melbourne, Australia

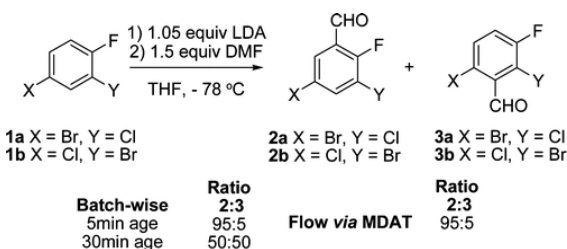
Various fullerene-based electron acceptor materials for organic photovoltaic applications were prepared via [3+2] and [4+2] cycloadditions using a continuous flow approach. The 1,3-dipolar cycloaddition of the tosylhydrazone precursor and the Diels-Alder cycloaddition of indene to either C₆₀ or C₇₀ under conventional batch reaction conditions were translated to the continuous flow process. By varying the residence time, temperature and equivalents of cycloaddition reagent, significant improvements in yields and reaction times were achieved over conventional batch processes.

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Magnetically Driven Agitation in a Tube Mixer Affords Clog-Resistant Fast Mixing Independent of Linear Velocity

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¹Jeffrey T. Kuethe

¹Department of Process Research, Merck
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²Chemical Process Development &
Commercialization, Merck
Manufacturing Division



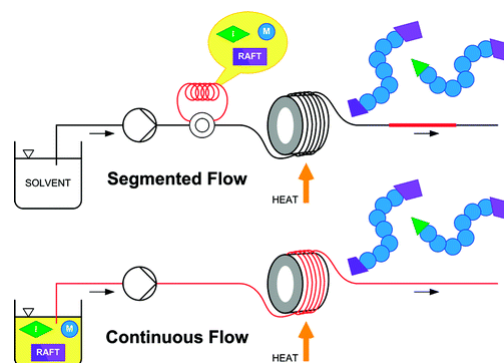
An economical and simple flow mixer based on magnetically driven agitation in a tube (MDAT) is reported. Mixing via MDAT compared favorably to both Tee and multilaminar mixers at low flow and was successfully used to screen and optimize two challenging organometallic reactions at low temperature without clogging or the need for high dilution.

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

Controlled RAFT Polymerization in a Continuous Flow Microreactor

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Simon Saubern
John Chiefari
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Controlled radical polymerization using the reversible addition–fragmentation chain transfer approach (RAFT) was successfully conducted under continuous flow processing conditions, provided that steel tubing was used to prevent quenching of the radical process by oxygen. A series of different monomers, including acrylamides, acrylates, and vinyl acetate, were polymerized to high conversions (between 80 and 100%) at temperatures between 70 and 100 °C using various initiators, solvents, and RAFT agents. Low dispersities, typically between 1.15–1.20, and average molecular weights similar to those of batch RAFT polymerizations were obtained. The methodology provides a facile, alternative scale-up route to conventional batch polymerization, which can be challenging because of the oxygen-sensitive nature of the RAFT process.

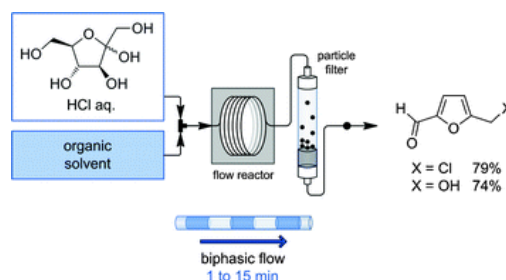
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Highly efficient dehydration of carbohydrates to 5-(chloromethyl)furfural (CMF), 5-(hydroxymethyl)furfural

(HMF) and levulinic acid by biphasic continuous flow processing

Malte Brasholz
Karin von Känel
Christian H. Hornung
Simon Saubern
John Tsanaktsidis

*CSIRO Materials Science & Engineering,
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Using a continuous flow reactor, the dehydration of D-fructose and other carbohydrates to 5-(chloromethyl)furfural (1) is achieved in reaction times as short as 60 s. The biphasic flow process allows for high-yielding multigram scale production of CMF (1) which is obtained with excellent purity after a simple extractive work-up. Efficient conversion of D-fructose into 5-(hydroxymethyl)furfural (2) and levulinic acid (6) is also demonstrated using flow reactor techniques.

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Thanks for your continued attention. See you in May.

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