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

Our last newsletter of the year is pretty packed, so here's a summary.

Contents

Thanks to all our users for another great year.

Product Announcements

METTLER TOLEDO FlowIR(TM) Integration

Vapourtec are pleased to announce a collaboration with METTLER TOLEDO.

The FlowIR(TM) can now be interfaced with the Vapourtec R Series system so that IR data characterising the reaction products can be logged and displayed by the Vapourtec system,

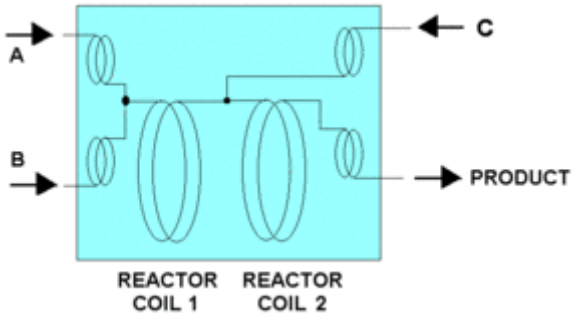
and even used to trigger collection of product peaks based on user criteria.

[See how it works]

Dual Core reactors

Vapourtec tube reactors (both heated and cooled) feature removable coil "cartridges" placed into a temperature controlled manifold.

In the case of the cooled reactor, the main reactor coil is preceded by reagent pre-cooling coils, and a cooled mixer.



Now it is possible to have two coils supplied on a single cartridge, enabling (for example) a 2 step cooled reaction (with a third reagent brought in after step 1) all controlled within a single cooled manifold.

This is especially useful for fast 2 step reactions where it is crucial that the reagents remain at the correct cooled temperature between cooled reaction steps

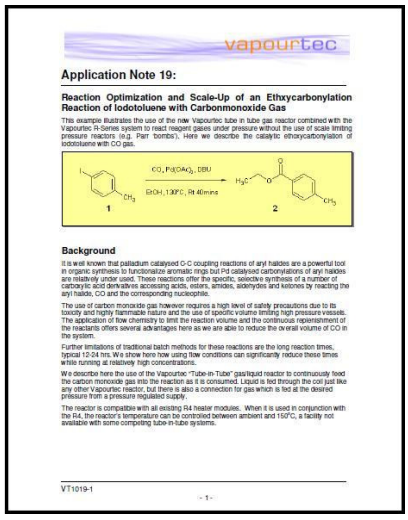
[More details]

Applications

New Application notes

For those curious to know how to use the new Vapourtec gas/liquid reactor there are now two new application notes available on the website.

They each show carbonylation reactions, and give full step by step details of how to both optimise and scale up a typical gas reaction.


vapourtec

Application Note 19:

Reaction Optimization and Scale-Up of an Ethxycarbonylation Reaction of Iodotoluene with Carbonmonoxide Gas

This example illustrates the use of the new Vapourtec tube in tube gas reactor combined with the Vapourtec R-Series system to react reagent gases under pressure without the use of scale limiting pressure reactors (e.g. Parr bombs). Here we describe the catalytic ethoxycarbonylation of iodotoluene with CO gas.

Background

It is well known that palladium catalysed C-C coupling reactions of aryl halides are a powerful tool in organic synthesis to functionalize aromatic rings but Pd catalysed carbonylations of aryl halides are relatively under used. These reactions offer the specific, selective synthesis of a number of carboxylic acid derivatives accessing acids, esters, amides, aldehydes and ketones by reacting the aryl halide, CO and the corresponding nucleophile.

The use of carbon monoxide gas however requires a high level of safety precautions due to its toxicity and highly flammable nature and the use of specific volume limiting high pressure vessels. The application of flow chemistry to limit the reaction volume and the continuous replenishment of the reactants offers several advantages here as we are able to reduce the overall volume of CO in the system.

Further limitations of traditional batch methods for these reactions are the long reaction times, typical 12-24 hrs. We show here how using flow conditions can significantly reduce these times while running at relatively high concentrations.

We describe here the use of the Vapourtec "Tube-in-Tube" gas/liquid reactor to continuously feed the carbon monoxide gas into the reaction as it is consumed. Liquid is fed through the coil just like any other Vapourtec reactor, but there is also a connection for gas which is fed at the desired pressure from a pressure regulated supply.

The reactor is compatible with all existing R4 heater modules. When it is used in conjunction with the R4, the reactor's temperature can be controlled between ambient and 150°C, a facility not available with some competing tube-in-tube systems.

VT1019-1

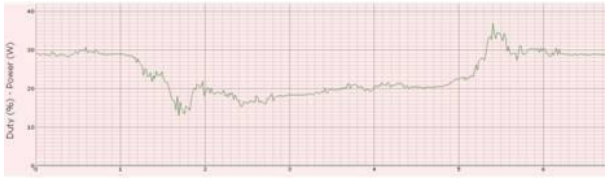
[Application note page]

Safely investigating and quantifying

exothermic reactions

Flow chemistry in a tube reactor offers far superior surface area to volume ratio (and hence heat transfer) compared to a round bottomed flask . And since all Vapourtec reactors are actively cooled, significant exotherms can be safely controlled.

But how can a reaction be safely run for the first time in flow if the scale of the exotherm is not yet known ?
This article explains how this can be achieved in a straightforward manner.



What is more, it is possible using the Vapourtec R Series and FlowCommander software to actually ***quantify*** the exotherm of a given reaction.

More detail

Events - 2011

International Congress on Green Process Engineering

6-8 Dec, 2011.
Kuala Lumpur, Malaysia
More details

Events - 2012

Flow Chemistry Europe

13-14 March , 2012
Munich, Germany
More details

Chemspec India

26 - 27 April, 2012
Mumbai, India
More details

Flow Chemistry Asia

25-26 October, 2012
Kuala Lumpur, Malaysia

Details to follow

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Publications

Vapourtec Users Reach 50 Publications

The number of peer reviewed scientific papers published by Vapourtec R Series users passed 50 in September (and that's not counting 5 recent new papers shown below).

Vapourtec would like to thank all users worldwide for their endeavours and for continuing to push the boundaries of what can be achieved in flow.

To see a complete list of publications (downloadable as a single PDF) follow the link below.

Vapourtec Publications Page

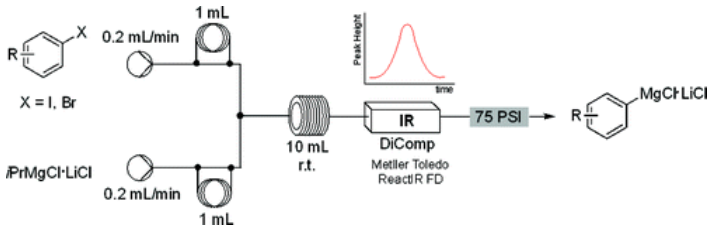
Flow Chemistry on TV

The Beilstein Journal of Organic Chemistry has published a video in which the technical approach used in a recent paper from the Prof Peter Seeberger's lab at the Max Planck Institute in Berlin (***Continuous flow photolysis of aryl azides: Preparation of 3H-azepinones***) is explained by the authors.

Click here to see the video

Continuous Preparation of Arylmagnesium Reagents in Flow with Inline IR Monitoring

Tobias Brodmann[1]
Peter Koos[1]
Albrecht Metzger[1]
Paul Knochel*[2]
Steven V. Ley*[1]



[1]Department of Chemistry, University of Cambridge, U.K.
[2]Department of Chemistry, Ludwig Maximilians-Universität München, Germany

A newly developed microscale ReactIR flow cell was used as a convenient and versatile inline analytical tool for Grignard formation in continuous flow chemical processing. The LiCl-mediated halogen/Mg exchange reaction was used for the preparation of functionalized arylmagnesium compounds from aryl iodides or bromides. Furthermore, inline IR monitoring was used for the analysis of conversion and possible byproduct formation, as well as a potential tool for elucidation of mechanistic details. The results described herein indicate that the continuous flow systems are effective for highly exothermic reactions such as the Grignard exchange reaction due to fast mixing and efficient heat transfer.

Click here to go straight to the publication

New Insights into Cyclobutenone Rearrangements: A Total Synthesis of the Natural ROS-Generating Anti-Cancer Agent Cribrostatin

(ROS=reactive-oxygen species)

Mubina Mohamed[1]
Théo P. Gonçalves[1]
Richard J. Whitby[1]
Helen F. Sneddon[2]
David C. Harrowven[1]

[1]Dept of Chemistry, University of Southampton, UK
[2]GSK Medicines Research Centre, Stevenage, UK

Aryl- and heteroarylcyclobutenone rearrangements proceed in excellent yield under continuous-flow conditions. The former shows a Hammett correlation with sigma1 providing strong evidence that electrocyclisation is the rate-determining step and has a late transition state. The reaction has been modelled by using DFT and CCSD(T) methods, with the latter giving excellent correlation with the experimental rate constant. A short and efficient total synthesis of cribrostatin 6, an anti-neoplastic and anti-microbial agent, provides a topical demonstration of the value of this method.

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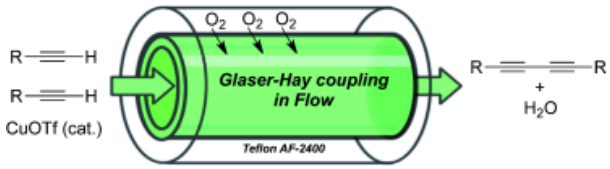
The Oxygen-Mediated Synthesis of 1,3-Butadiynes in

Continuous Flow: Using Teflon AF-2400 to Effect Gas/Liquid Contact

Trine P. Petersen (1,2,3)
Dr. Anastasios Polyzos (1,4)
Dr. Matthew O'Brien (1)
Dr. Trond Ulven (2)
Dr. Ian R. Baxendale (1)
Prof. Steven V. Ley (1)



1 Whiffen Laboratory, University of Cambridge, UK
2 Department of Physics and Chemistry, University of Southern Denmark
3 Discovery Chemistry and DMPK, H. Lundbeck A/S,Denmark
4 CSIRO, Materials Science and Engineering, Australia

The gas is always greener: A continuous flow Glaser-Hay coupling reaction system, mediated by molecular oxygen, is developed based on a tube-in-tube gas/liquid reactor/injector. The system uses a semi-permeable Teflon AF-2400 membrane to effect rapid gas/liquid contact in flow, affording homogeneous solutions of oxygen. Measurements of out-gassing downstream of the back-pressure regulator indicate the onset of saturation is reached after ca. 16 seconds.

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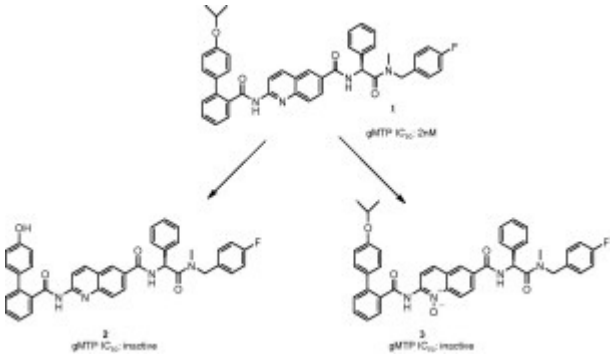
Lead Diversification 2: Application to P38, gMTP and lead compounds

M. Abid Masood [1]
Marc Bazin[2]
Mark E. Bunnage[1]
Andrew Calabrese[3]
Mark Cox[1]
Sally-Ann Fancy[1]
Elizabeth Farrant[1]
David W. Pearce[1]
Manuel Perez[1]
Laure Hitzel[1]
Torren Peakman[1]



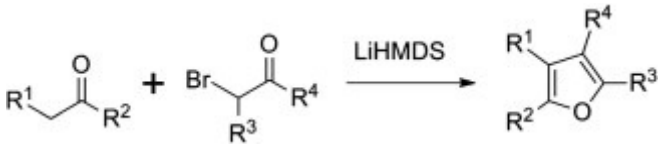
[1] Worldwide Medicinal Chemistry, Pfizer, UK
[2] Hepatochem, Cambridge, MA, USA
[3] Celgene San Diego, USA

Lead Diversification is a new technology platform developed at Pfizer for the functionalization of drug molecules using C-H activation. We describe its application to some drug programs such as P38 and gMTP and the development of some new plate based screens including a fluorination screen.

Click here to go straight to the publication

A continuous-flow synthesis of annulated and polysubstituted furans from the reaction of ketones and a-haloketones

Mark York
CSIRO Materials Science and Engineering, Australia
Cooperative Research Centre for Polymers, Notting Hill, Australia



A synthesis of di-, tri- and tetra-substituted furans from reaction of the corresponding ketones and a-haloketones with LiHMDS is reported. Reaction under continuous-flow conditions gave increased yields and removed the need for external cooling when compared to the unoptimised batch conditions.

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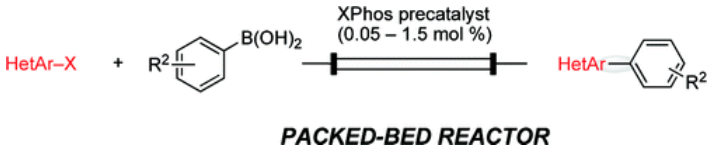
Suzuki-Miyaura Cross-Coupling of Heteroaryl Halides and Arylboronic Acids in Continuous Flow

Timothy Noël and Andrew J. Musacchio
Department of Chemistry, MIT, USA



General continuous-flow conditions for the Suzuki-Miyaura cross-coupling of heteroaryl halides and (hetero)arylboronic acids have been developed. A wide range of heterobiaryl products is obtained in excellent yields (20 examples) employing low catalyst loadings (0.05-1.5 mol % Pd).

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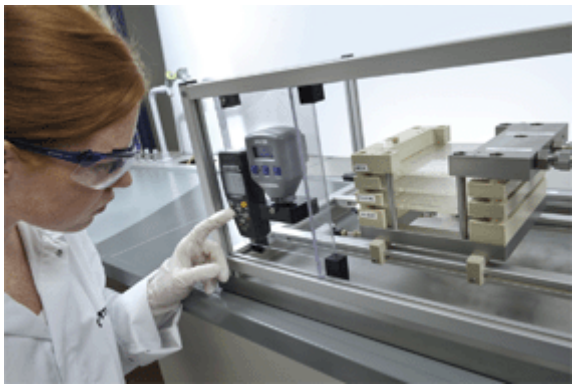
Reviews

Continuous flow reactors: a perspective

Charlotte Wiles and Paul Watts
University of Hull



With aspects of continuous processing featuring heavily in efforts towards increasing the 'green' prospects of pharmaceutical and fine chemical manufacturing, this article focuses on the developments made into the application of continuous flow reactors for sustainable

chemical research and production.

FREE TO DOWNLOAD

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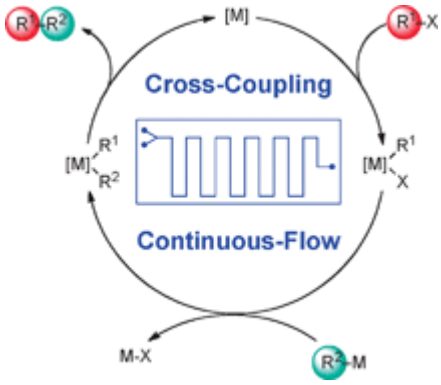
Cross-coupling in flow

Timothy Noël
Stephen L. Buchwald

MIT, USA



Until recently, cross-coupling reactions have been exclusively performed in batch processes. With the advent of microfluidics, significant effort has been devoted to develop a wide variety of continuous-flow techniques to facilitate organic synthesis. In this critical review, we attempt to give an overview of the different continuous-flow methodologies that have been developed and utilized for cross-coupling reactions. In addition, we attempt to point out the advantages of continuous-flow when compared with their batch counterparts (246 references).

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