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Flow Chemistry Highlights

Flow Chemistry Network

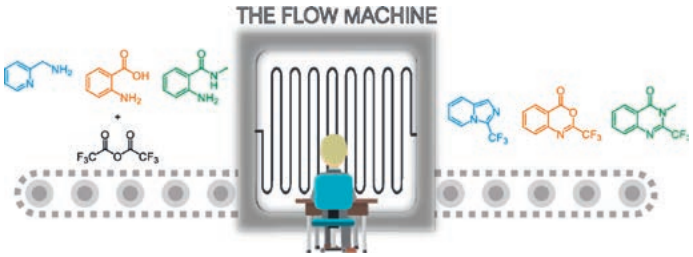
Review of recent literature on flow chemistry. Selected topic: **Academic - Industrial Partnerships**

A Novel and Efficient Continuous-Flow Route to Prepare Trifluoromethylated N-Fused Heterocycles for Drug Discovery and Pharmaceutical Manufacturing

L. Amini-Rentsch, E. Vanoli, S. Richard-Bildstein,* R. Marti, G. Vilé, *Ind. Eng. Chem. Res.* **2019**, 58, 10164–10171, https://doi.org/10.1021/acs.iecr.9b01906

In this collaboration between the University of Applied Sciences Western Switzerland and Idorsia Pharmaceuticals, the researchers explore the synthesis of trifluoromethylated *N*-fused heterocycles in flow. Two known batch routes were first assessed for safety and then optimized in automated DoE campaigns using a Vapourtec flow chemistry system. A variety of heterocycles were synthetized in good yields using a two-step route as well as one-pot approach, which due to safety reasons was unlikely to be implemented in a batch reactor. Scale-up of a selected example *via* one-pot synthesis achieved 60% isolated yield with productivity of 1 g/h and a total uninterrupted run time of 8 h, highlighting the robustness of the procedure and ease of scale-up in flow. Finally, the authors investigated the cost and green metrics of the available syntheses. Overall, the one-pot reaction proved to be more sustainable and cost-effective than the two-step approaches in batch and flow, showcasing how the inherent safety of flow setups may give access to greener routes inaccessible to batch methods.

Author's comments*:
"Described one-pot flow methodology enables the access to a wide range of novel CF_3-containing heterocycles in a green, robust, and cost-efficient manner and has the potential to find widespread applications in pharmaceutical and agrochemical laboratories."

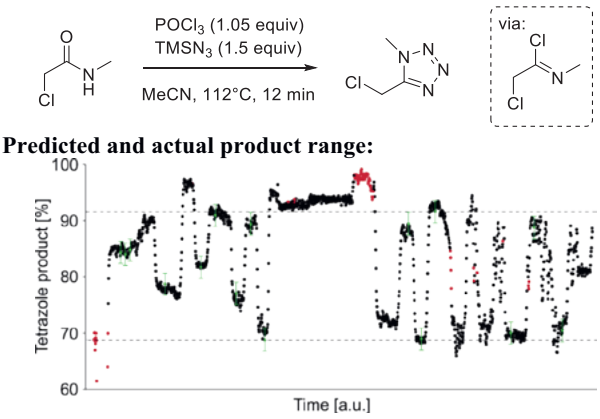


Intensified Continuous Flow Synthesis and Workup of a Key Tetrazole Intermediate Enhanced by Real-time Process Analytics

P. Sagmeister, D. Kaldre, J. Sedelmeier,* C. Moessner, K. Püntener, D. Kummli, J. D. Williams, C. O. Kappe, *Org. Process Res. Dev.* **2021**, *25,* 5, 1206–1214, https://doi.org/10.1021/acs.oprd.1c00096

Continuous flow processing presents a safer option for the handling of dangerous reagents and intermediates, due to the small reactive inventory and lack of a reactor headspace. In this collaboration between the University of Graz and F. Hoffmann-La Roche, the authors elaborate on the formation of 1,5-tetrazole moieties, starting from an amide, activated using $POCl_3$ to its corresponding imidoyl chloride, which reacts with trimethylsilyl azide. The synthesis of tetrazoles is challenging in a manufacturing environment and special care must be taken to prevent the formation of shock-sensitive and explosive metal azide salts, precluding the use of standard reactors and impellers. Acid-mediated synthetic methods are especially difficult to handle on large scale, due to the formation of highly volatile, toxic and explosive hydrazoic acid.
During the optimization phase, inline NMR analysis was used in troubleshooting, which was then transitioned to inline quantitative FTIR on manufacturing scale.
Finally, this protocol was used to synthesize a selection of substrates, including the API pentylene-tetrazole and an advanced intermediate toward cilostazol.

Author's comments*:
"The outlined work is a masterpiece of handling dangerous chemistry in small reactive inventory in the absence of a reactor headspace and as such is truly enabling."



Would you like to propose a Flow Chemistry Highlight topic here?
Please contact Agnieszka Ladosz or Benjamin Martin, E-mail: agnieszka.ladosz@idorsia.com; benjamin.martin@novartis.com

Enantio-Complementary Continuous-Flow Synthesis of 2-Aminobutane Using Covalently Immobilized Transaminases

C. M. Heckmann, B. Dominguez, F. Paradisi*, *ACS Sustainable Chem. Eng.* **2021**, *9*, 4122–4129, https://doi.org/10.1021/acssuschemeng.0c09075

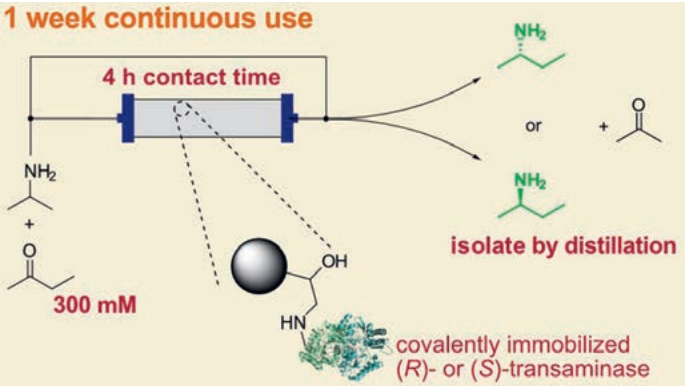
Transaminase enzymes are a proven tool to prepare chiral amines, but the synthesis of amines from ketones with similarly sized groups flanking the carbonyl is challenging. In this collaboration between the University of Nottingham and Johnson Matthey UK, the authors identify two enzymes capable of the feat of enantio-discrimination between the flanking methyl- and ethyl-groups of 2-butanone. Notably a strategic point mutation in the wild-type transaminase could enhance the enantioselectivity from an e.e. of 45 to >99.5%.

Immobilisation of both candidates enabled the multigram scale-up in continuous flow of both (*S*)- and (*R*)-2-aminobutane from 2-butanone and isopropylamine. The setup was operated for 1 week and the space-time yield (mol.mL^{-1}.h^{-1}) was demonstrated as being an order of magnitude higher than the batch setup with soluble enzyme.

E-factor calculation confirmed that this process, which was solvent-free other than water and avoided kinetic resolution, was a sustainable approach to small molecule chiral amine synthesis.

Author's comments*:

"Working closely with Johnson Matthey on challenging substrates which are relevant in agrochemical applications, has given us the opportunity to challenge transaminases differently through computer-assisted protein design. The implementation of the whole process in flow has been really successful."



Continuous Flow Acylation of (Hetero)aryllithiums with Polyfunctional N,N-Dimethylamides and Tetramethylurea in Toluene

D. Djukanovic, B. Heinz, F. Mandrelli, S. Mostarda, P. Filipponi, B. Martin,* P. Knochel, *Chem. Eur. J.* **2021**, *27*, 1–6, https://doi.org/10.1002/chem.202102805

Ketones are commonplace functional groups in material-, agro- and medicinal-chemicals and as such the collaboration between the Ludwig Maximilian University of Munich and Novartis Pharma Basel aimed to prepare ketones by straightforward and mild acylations of organolithium species. Complicating the strategy is over-reaction of the ketone product with a second equivalent of organolithium leading to alcohols.

Choosing to eschew Weinreb amides (costly, non-commercial, toxic and the amine is explosive as free-base), the authors identified *N*,*N*-dimethylamides as atom-economic electrophiles in combination with *sec*-BuLi activated (hetero)aryl bromides. A key discovery was that toluene as solvent suppressed the over-reaction as well as mitigating proton-quenching from electrophiles with enolizable amides, albeit with inclusion of 1eq. THF to maintain a rapid bromine-lithium exchange.

Complementary was the use of continuous flow equipment to maximize yields and throughput of a range of ketones prepared on the minute time-scale. Finally tetramethylurea was identified as a useful C1-building block (CO) to prepare non-symmetrical ketones in a combination of continuous and semi-batch processing.

Author's comments*:

"Together with our earlier collaborative acylation study with esters, the discovery that simple amides can be selectively acylated in toluene with a practical flow setup is set to transform our chemical R&D synthesis efforts whenever we see ketones in our intermediates or drug substances."