Fluorination Chemistry Performed in a Modular Flow Reactor

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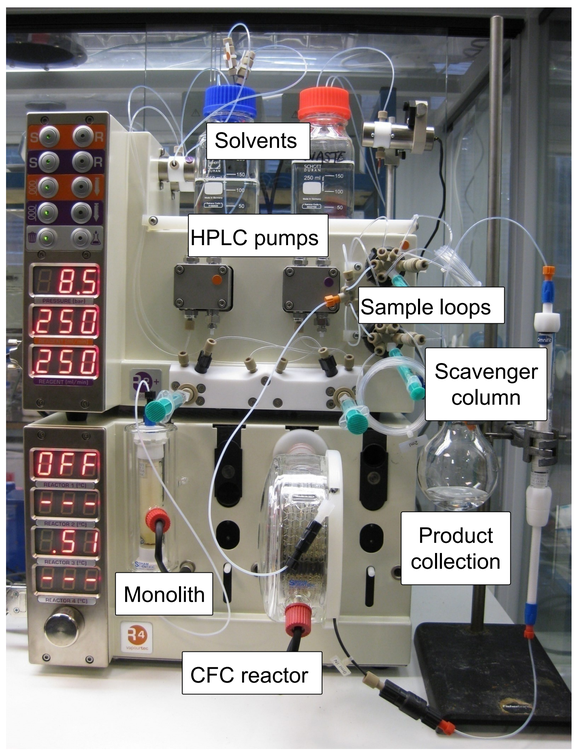
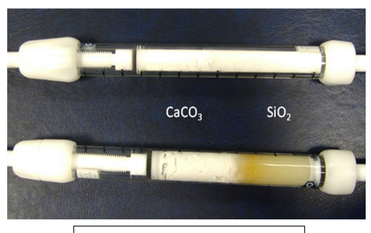
Introduction to Flow Chemistry

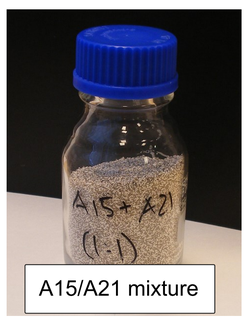
The Ley group has a long-standing interest in the development of novel concepts and technologies in organic chemistry and their application to natural product synthesis as well as methodology projects [1]. Our previous research involving the use of microwave reactors as well as polymer-supported reagents, catalysts and scavengers demonstrated that chemical synthesis can greatly benefit from these techniques in terms of reduced reaction times, more efficient work-ups and increased product yields and purities. Furthermore, we developed an interest in the use of flow reactors to allow continuous and automated processing with in-line purification using immobilised species thereby avoiding time-consuming work-up procedures. These flow reactors permit the safe and convenient handling of hazardous, unstable or highly toxic reagents and intermediates within a contained environment. More recently, we have developed flow techniques for single and multi-step transformations involving azides [2] and several fluoride-species [3]. Fluorination reactions have proven to be of particular interest for the synthesis of pharmaceuticals and agrochemicals. However, the fluorination methods used in the standard batch processes employ highly toxic and hazardous reagents and produce problematic side-products such as fluorine gas or hydrogen fluoride. Our approach used benign fluorinating reagents in a contained flow reactor, concurrently with reliable in-line purification procedures. This allowed us to conveniently evaluate and establish safe and easy flow procedures for a variety of important fluorination reactions.

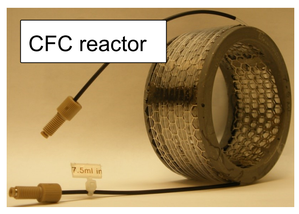
Vapourtec R2+R4 flow system





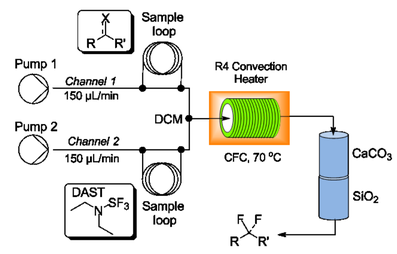
Scavenger columns for DAST reactions





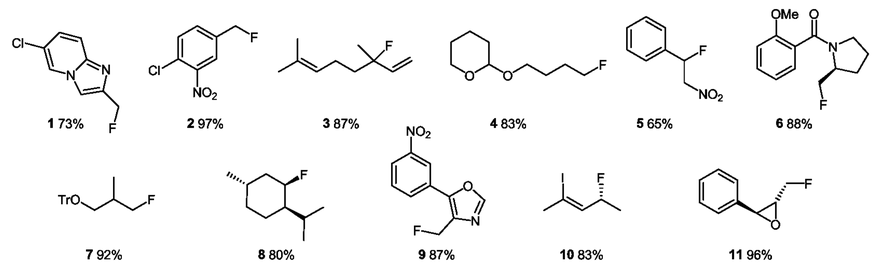
The commercially available Vapourtec R2+R4 system was used to conveniently perform all fluorination reactions. The inert fluorinated polymer in both the sample loops and the tubing material was resistant and robust to the corrosiveness of some of the reagents used.

Nucleophilic Fluorination with DAST

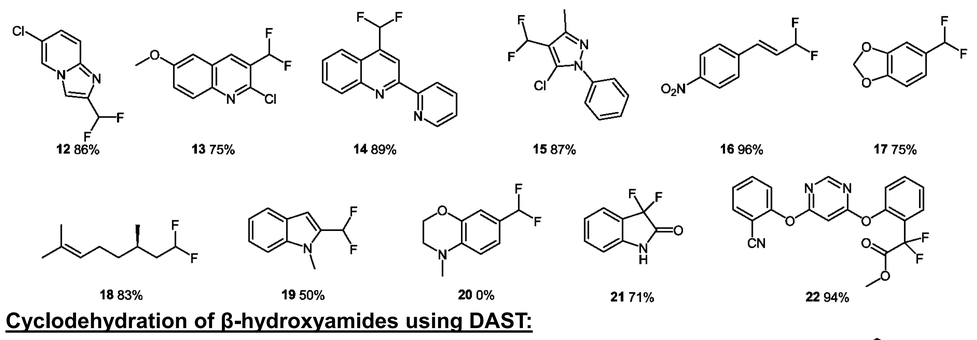


1) Inert sample loops of R2+R4 system are loaded with stock solutions in DCM.
2) Required temperatures range from 50-90°C.
3) In-line purification uses $CaCO_3$/SiO_2 as mixed-bed scavengers to remove inorganic fluoride, excess DAST and its by-products.
4) Products were obtained in high yields (>75%) and high purities (>95% by ^{1}H-NMR, fluoride contamination ~10 mg/mL).

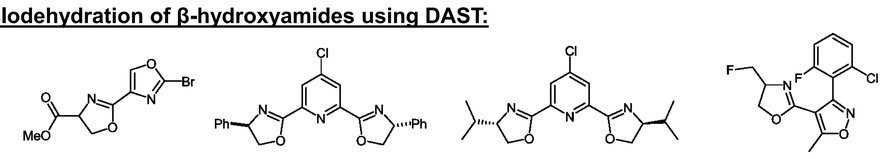
Monofluorination of alcohols:



Difluorination of aldehydes and ketones:

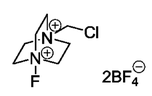


Cyclodehydration of β-hydroxyamides using DAST:

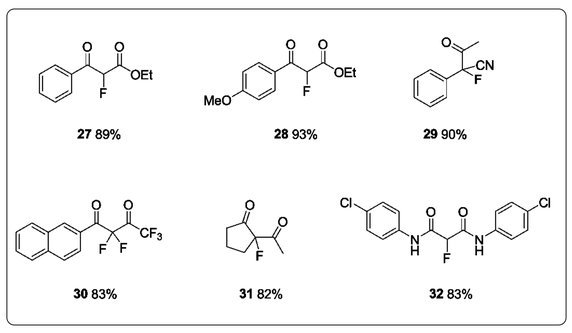


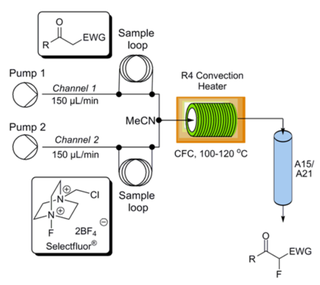
Selectfluor for α-Fluorination and Ritter-reactions

1) MeCN was found to be best to dissolve the ionic Selectfluor™ reagent.
2) High temperatures (100-120°C) are advantageous to obtain high and quick conversion (30-60 min).
3) Mono- and di-fluorination is possible. Work-up uses a mixture of A15/A21 in an Omnifit-column.

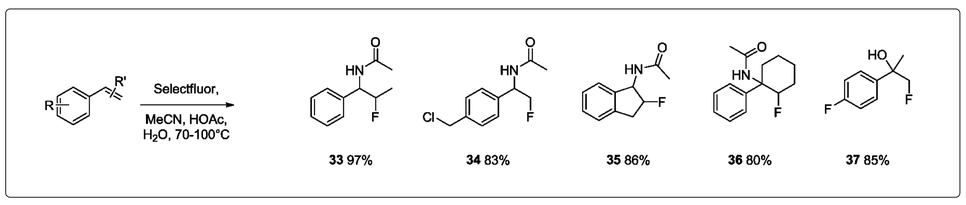


Selectfluor™





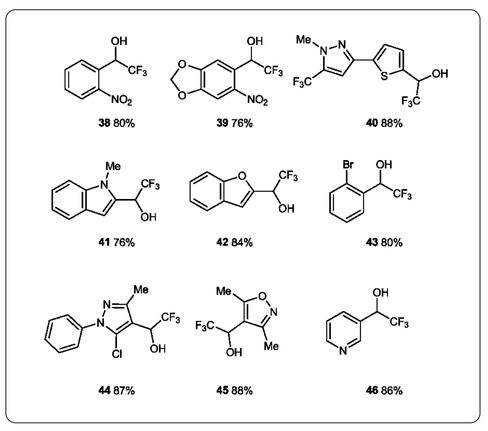
In addition to the α-fluorination described above the Selectfluor™ reagent can also be used to perform fluoro-Ritter reactions in flow. Using acetonitrile in the presence of wet acetic acid the conversion of various electron-rich styrenes to the corresponding Ritter products can be affected. Interestingly, this reaction allows the simultaneous introduction of fluorine and a protected amine or hydroxyl functionality (**37**).

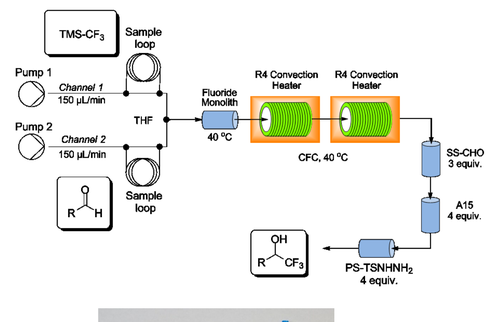


Ruppert's Reagent for Trifluoromethylation reactions

Having established flow methods for mono- and di-fluorination we were also interested in the incorporation of trifluoromethyl groups, which can be accomplished using Ruppert's reagent (TMS-CF_3). In order to activate this reagent a fluoride species (TBAF, KF, CsF) is typically required. However, such an additional reagent has to be removed after the reaction, which led us to the development of a novel fluoride monolith. Such an ion-exchange monolith is a higher-loading and conveniently formatted material for conducting flow chemistry that can be re-used many times by reloading with aqueous sodium fluoride solution.

In order to evaluate this concept a small collection of aldehydes has been converted to the corresponding CF_3-compounds using Ruppert's reagent in flow:





Monolith in Omnifit-column

References and Acknowledgements

References: (1) The Changing Face of Organic Synthesis, S. V. Ley and I. R. Baxendale, *Chimia*, **2008**, *62*, 162-168. **(2)** A Modular Flow Reactor for Performing Curtius Rearrangements as a Continuous Flow Process, Marcus Baumann, Ian R. Baxendale, Steven V. Ley, Nikzad Nikbin, Christopher D. Smith, Jason P. Tierney, *Org. Biomol. Chem.*, **2008**, *6*, 1577-1586. Azide Monoliths as Convenient Flow Reactors for Efficient Curtius Rearrangement Reactions, Marcus Baumann, Ian R. Baxendale, Steven V. Ley, Nikzad Nikbin, Christopher D. Smith, *Org. Biomol. Chem.*, **2008**, *6*, 1587-1593. **(3)** The Use of Diethylaminosulfur Trifluoride (DAST) for Fluorination in a Continuous-Flow Microreactor, Marcus Baumann, Ian R. Baxendale, Steven V. Ley, *Synlett*, **2008**, *14*, 2111-2114.

Acknowledgements: Many thanks to Prof. Steven V. Ley, Dr Ian R. Baxendale, Dr Laetitia J. Martin, Dr Nikzad Nikbin and the ITC team for their help and guidance. MB would also like to thank the Cambridge European Trust and the Ralph Raphael studentship for funding. We would also like to thank Vapourtec for the use of their equipment and EPSRC, GSK, Novartis, Pfizer and Syngenta for their continued support of our laboratory.