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Review

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Selective Continuous Flow Processes Using Fluorine Gas

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ABSTRACT: The use of continuous gas−liquid flow reactors for processes involving fluorine gas is reviewed. Falling film, microbubble, and laminar flow reactors that have been adapted to carry out direct fluorination reactions are described, and a range of selective fluorination reactions involving direct fluorination of a variety of aromatic, dicarbonyl, diester and benzaldehyde derivatives are presented as well as related continuous flow oxidation processes (such as epoxidation reactions and the transformation of amines to nitro derivatives) involving fluorine gas.

1. INTRODUCTION

Continuous flow reaction techniques, used widely by industry for the large-scale production of many chemical products for some considerable time,[1] are now being adopted by synthetic chemists as part of research and development programmes,[2,3] and a variety of commercially available flow reactor systems are available to meet the varied requirements of the discovery laboratory.[4] Many well-established synthetic organic chemistry transformations have been adapted to flow reactor regimes,[3] and the advantages of using continuous flow processes over conventional batch techniques, such as high throughput; use of very small quantities of material when appropriate; reduced waste streams; low manufacturing, operation, and maintenance costs; low power consumption; increased precision and accuracy and disposability, have been well discussed[2,3] and continue to be debated.[5] Miniaturisation may also lead to increased performance of a system due to optimisation of contact between reagents because of very rapid mixing in such devices. The concept of 'scale-out' by running many reactors in parallel is also very appealing, where bench operation would exactly mirror the manufacturing situation, thus reducing resources required for good manufacturing practice (GMP) accreditation.

The introduction of fluorine atoms into organic molecules can have a profound effect upon the physical, chemical, and biological properties of a wide range of molecular systems,[6−9] and such changes have been used to great effect in all sectors of the chemical industry.[9,10] Many pharmaceuticals and agrochemicals, such as Prozac, Lipitor, and Ciprofloxacin, owe their potent and commercially very valuable biological activities to the presence of fluorine atoms within their molecular structures.[10] Indeed, the use of continuous flow methodologies for fluorination reactions using diethylaminosulfur trifluoride (DAST), for the transformation of alcohols and ketones to alkyl fluoride and difluoromethylene derivatives, respectively, and Selectfluor for electrophilic fluorination processes has been reported recently.[11−13] For large-scale synthesis and manufacture of fluorinated derivatives, inexpensive reagents such as hydrogen fluoride, potassium fluoride, or fluorine gas are preferred, and in particular, HF and KF are used extensively for the production of a wide array of fluorinated intermediates and life-science products on the multiton scale.[9,10] However, problems with handling highly corrosive and toxic reagents such as HF make the development and successful application of easy-to-use selective fluorinating agents a valuable research and development goal.

Direct fluorination of organic systems offers a potentially very efficient means of introducing fluorine atoms into a particular target molecule by transformation of carbon−hydrogen bonds to carbon−fluorine bonds directly.[14−16] Such strategies do not require multistep prefunctionalisation of the substrate and, consequently, are far more resource efficient. Direct fluorination is, however, highly exothermic (−430 kJ mol^{-1} for the replacement of hydrogen bonded to sp_3 carbon),[14] and means of dissipating the high heat of the reactions by dilution of fluorine in nitrogen (typically 10% mixtures of fluorine in nitrogen are used and are commercially available), efficient reaction cooling, and choice of appropriate solvent are required to carry out selective fluorination.[14−16] Fluorine gas, although used in the semiconductor fabrication and nuclear power industries on the large scale, is not a reagent that has been used for the manufacture of many chemical products. However, the production of 5-fluorouracil by direct fluorination of uracil in acetic acid[15] and the production of a fluoroketoester used as an intermediate in the production of Voriconazole (V-Fend, Pfizer) by selective, direct fluorination techniques[17] offer some indication of the potential for using fluorine gas on the manufacturing scale for atom-efficient, inexpensive synthesis of fluorinated derivatives.

The potential advantages of applying continuous flow techniques to selective processes involving highly reactive or very toxic reagents in highly exothermic reactions such as those using fluorine gas was recognised at an early stage in the development of laboratory-scale continuous flow reactor chemistry because of the enhanced safety in handling small quantities of toxic material within the reaction channel at any one time and increased reaction control. In particular, it was thought that reactions involving fluorine gas would be an ideal test reaction that would demonstrate the benefits of using continuous flow processes in the laboratory, and beginning in the early 1990s, several research groups began to develop gas−liquid flow reactors that could be used for direct fluorination

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reactions. This brief review aims to provide an overview of the various reactor types used for selective continuous flow processes involving fluorine gas and direct fluorination processes that have been subsequently carried out in gas–liquid flow regimes.

2. CONTINUOUS FLOW GAS–LIQUID REACTORS FOR FLUORINE

2.1. Falling Film Reactor. The falling film reactor (Figure 1) is a gas–liquid reaction device that was adapted for use with

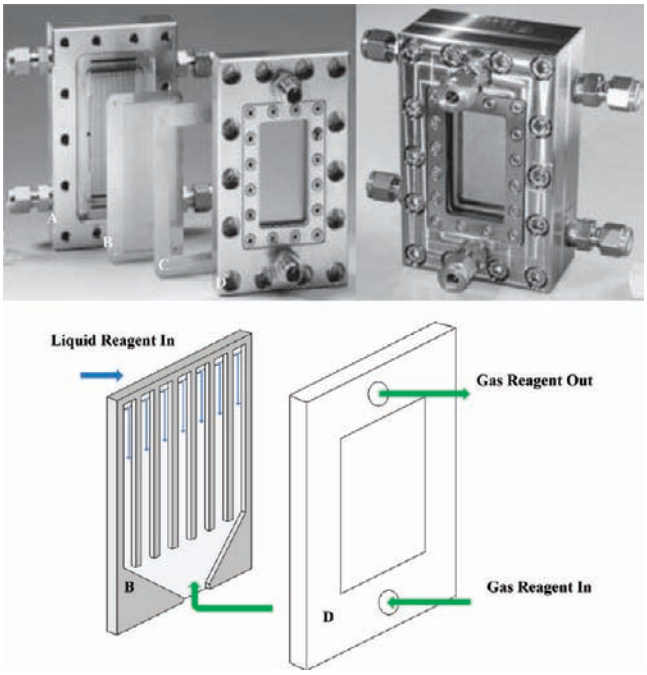

Figure 1. Falling film reactor. (Top) Disassembled falling film reactor. [A] Base plate (with heat exchanger and liquid inlet/outlet slits). [B] Reaction plate. [C] Contact zone mask. [D] Top plate (with window and gas inlet/outlet valves). (Middle) Assembled falling film reactor. (Bottom) Schematic diagram showing fluid flow.

fluorine gas at the Institut für Mikrotechnik (IMM) in Germany.[18–20] The reactor consists of four components: the base plate [A], which houses the liquid inlet/outlet valves and integrated heat exchanger, the reaction plate [B], a contact zone mask [C], and the top plate [D], which is the fluorine gas chamber and houses the gas inlet/outlet valves.

The main component is the stainless steel reaction plate [B] which has several micro channels fabricated into the steel surface. Depending on the plate, these range from widths of 100–1200 μm and depths of 100–600 μm. Each channel has an inlet hole at the top of the device, which aligns with the liquid inlet slit of the base plate [A]. Therefore, when the liquid is injected through the slit, fluid is evenly distributed into each reaction channel and flows down the channels under gravity. The end of the reaction channels are aligned with the liquid outlet slit of the bottom plate. The top gas chamber plate [D] is placed over the reaction channels and the gas is injected through a diffuser at the bottom of the chamber, which ensures that the gas is distributed throughout the chamber homogeneously. The gas flows in an upward motion over the falling liquid film, enabling reaction to occur, and excess gas is released through the outlet gas valve at the top of the reactor whilst products are collected from the outlet at the lowest point of the base plate. The falling film reactor is capable of producing liquid films with a depth of just 15 μm, which corresponds to a specific phase interface of 20,000 m^2 m^{-3}.[18]

2.2. The Microbubble Reactor. The microbubble reactor (Figure 2) was also developed by IMM and their collabo-

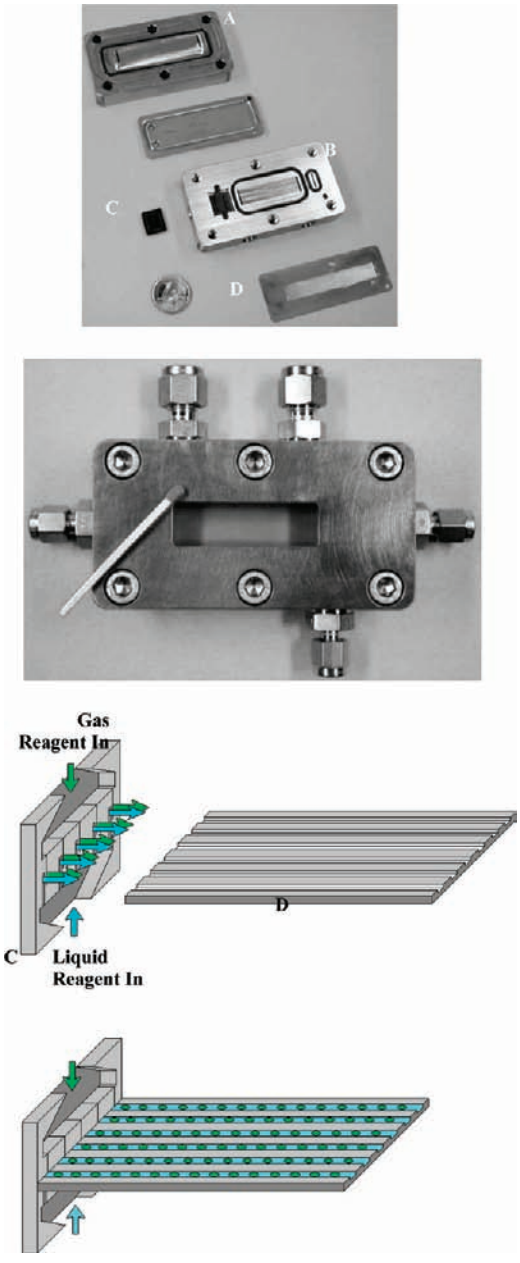

Figure 2. Microbubble Reactor. (Top left) Disassembled microbubble reactor [A] Top housing plate. [B] Microdispersion unit. [C] Bottom housing plate. [D] Reaction channel plate. (Top right) Assembled microbubble reactor. (Bottom) Diagram of components: static microdisperser unit [C] and the reaction channel plate [D].

rators[18] and is operated in a horizontal position. It consists of four components, the top and base plates [A and B] which have integrated heat exchangers, the microdispersion gas/liquid inlet unit [C], and the reaction plate [D].

The central components of this reactor are the static microdisperser unit [C] and the reaction channel plate [D]. The microdisperser unit is made of a nickel/copper alloy

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through which the fluorine gas and liquid substrates are added at opposite ends of the unit. Uniform distribution of the reactants is achieved by the small size of the inlet micro dispersion channels, which are no larger than 5 μm for the gas and 20 μm for the liquid. The microdispersion unit [C] sits vertically in the reactor and attached is the perpendicular stainless steel reaction channel plate [D] consisting of 64 reaction channels of 20 × 600 μm. The gas and liquid reactants are fed into the reaction channels via the microdispersion unit. The reaction plate and microdispersion unit are locked between the housing plates [A] and [B], which also function as heat exchangers whilst the base plate also houses the reactant outlet slit to collect for product collection. This reactor is designed for rapid reactions of less than one second and by varying the gas and liquid flow rates, flow regimes such as slug, annular and spray flow can be obtained.

2.3. Continuous Laminar Flow Reactors. In 1999, the Durham Fluorine group described the design of a reactor specifically constructed for the manipulation of elemental fluorine.[21,22] The reactor consists of three parts (Figure 3); a solid block of nickel metal (120 mm ×27 mm ×5 mm) with a 100 mm long, 500 μm diameter reaction channel etched into its surface [A]. Attached to the surface of the nickel channel is a transparent solid polychlorotrifluoroethylene (PCTFE) block (120 mm ×27 mm ×5 mm) [B] which is held in place via a bolted stainless steel block (120 mm ×27 mm ×2 mm) [C]. The PCTFE block has three holes (1000 μm diameter) drilled into it which align with the reaction channel and allow stainless steel tubing (1000 μm external diameter and 800 μm internal diameter) to be inserted into the PCTFE block, which sits just above the reaction channel allowing the gas and liquid reactants to be added via the two inlet ports and the product to be collected at the outlet. The temperature of the reaction block is controlled via a copper channel which is threaded through the nickel block and attached to an external, circulating cooling cryostat.

Elemental fluorine is added to the first inlet and is mixed with the liquid reagent which is added to the second inlet. Products and excess reagents are then received in a collection vessel via the outlet tube. Mixing in the reactor proceeds by laminar or 'pipe' flow, as opposed to intermittent or 'slug' flow, which also ensures excellent heat transport away from the reaction zone to the nickel block.

To perform effective scale-out of continuous flow gas–liquid reactions, a vertical modular flow reactor system was designed and constructed which allows many reaction channels to be supplied from single independent reservoir sources of fluorine and substrate solutions via slits that are perpendicular to the multiple reaction channels.[23] The reactor consists of five parts (Figure 4): the steel block [A] has two substrate reservoirs (40 mm and 30 mm diameter for the gas and liquid, respectively), cut through the width of the top end of the block, and a collection reservoir (20 mm diameter) at the bottom of the block. These have slits cut along their width which emerge at the surface of the block. The nickel base plate [B] also has slits cut into it which exactly align with the steel block slits and provides the base of the reaction channel.

The actual reaction channels themselves, typically 500 μm wide, are cut into a stainless steel plate and the depth of the channels are therefore dictated by the thickness of the plate, which is also typically 500 μm. Channel plates consist of typically 9, 18, or 30 channels. A transparent PTCFE block is then placed onto the reaction plate which completes the

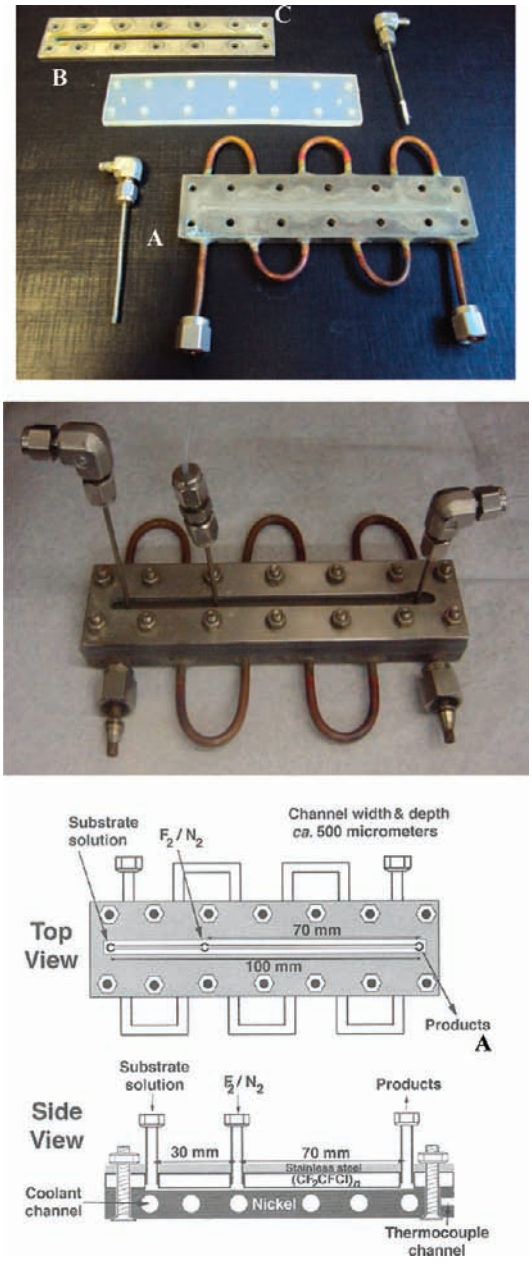

Figure 3. Durham single channel laminar flow reactor. (Top Left) Disassembled horizontal single channel reactor: [A] nickel block with reaction channel and copper cooling pipe, [B] PCTFE block, [C] top housing plate. (Top Right) Assembled flow reactor. (Below) Schematic diagram.

reaction channel, and a top stainless steel window plate is bolted onto the base plate which compresses the whole unit together. The reactants are added to the reservoirs of the nickel block [A] that, once filled, flow through the slits to the surface of the block and down the reaction channels. The volume of the reservoirs is substantially greater than the sum of the volumes of the channel paths, therefore, ensuring equal fluid distribution into each individual channel. Upon entry to the channels, the gas and liquid flow along the channel paths in a laminar flow regime enabling reaction to occur and, at the end of each channel, the product flows into the product reservoir slit, which can then be collected through an exit tube.

As with the horizontal reactors, piping threaded through the reaction block can be connected to an external circulating

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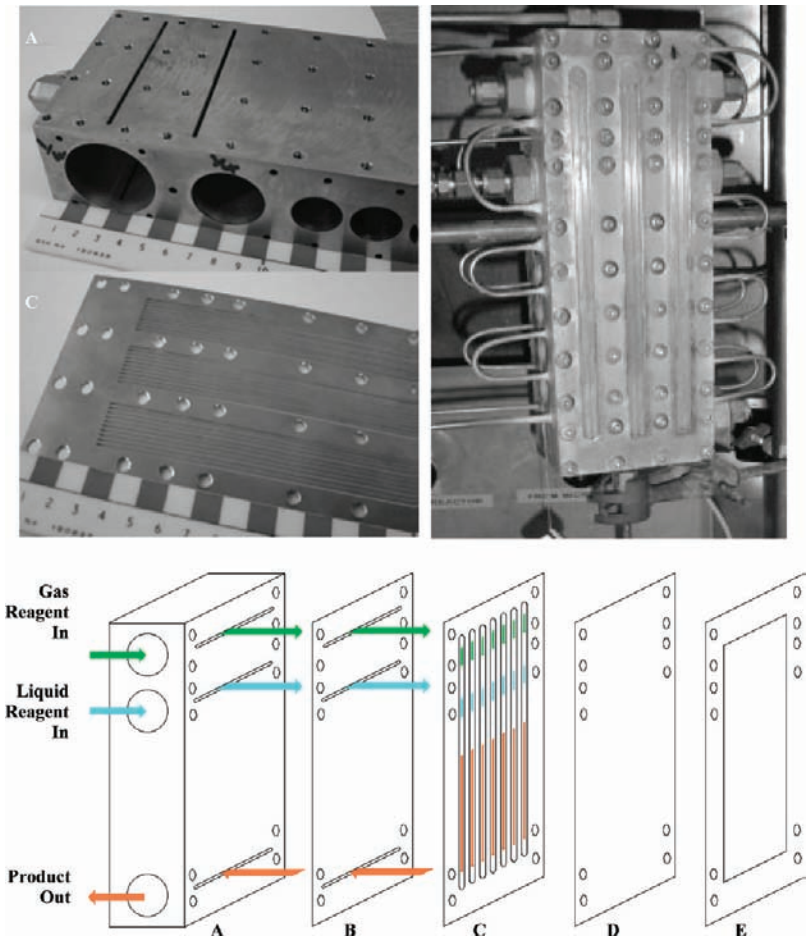


Figure 4. Multichannel continuous laminar flow reactor. (Left top) The steel reservoir block [A]. (Left middle) Reaction channel plate [C]. (Right) Assembled vertical reactor. (Bottom) Diagram of flow.

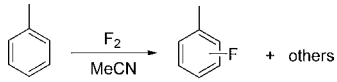
cryostat to allow for thermal control of the reaction. Continuous operation for various fluorination processes, such as the fluorination of β-ketoesters such as 2-fluoro ethyl acetoacetate described below, over an extended time period of 150 h have been performed with no loss of yield or conversion and with each channel able to synthesize ~0.3 g of material per hour, approximately 220 g of product can be synthesized per day using the 30-channel reaction plate.[23]

3. SELECTIVE DIRECT FLUORINATION REACTIONS OF ORGANIC SUBSTRATES IN FLOW

Continuous flow reactor regimes have been used for the selective direct fluorination of a range of aromatic, benzaldehyde, dicarbonyl, and diester substrate classes, and an overview of these processes is included below. All of the selective fluorination processes described below were carried out using a laminar flow system unless stated otherwise.

3.1. Fluorination of Aromatic Systems. Initial experiments explored the direct fluorination of toluene[18,24] which was found to give a mixture of fluoroarenes bearing fluorine at ortho, meta, and para positions with yields up to 28% (Scheme 1). These were benchmarked against the laboratory bubble column which gave, at best, yields of 8% monofluorination. As would be expected for an electrophilic process, the ortho and para isomers were the predominant products obtained, although other polyfluorinated systems and significant amounts of tar were also formed. Of course, tar formation should ideally be avoided as this can lead to channel blockage in very small microchannels and subsequent device failure.

Scheme 1. Direct fluorination of toluene using the falling film reactor



28%, *o* : *m* : *p*, 5 : 1 : 3

Fluorination of aromatic derivatives bearing an electron-donating substituent and an electron-withdrawing substituent at the 1- and 4-positions respectively, thereby directing electrophilic attack towards the most activated 2-position in an electrophilic process, are much more selective[25] and have been carried out in continuous flow fluorination regimes using the laminar flow reactor system (Scheme 2).[22,23] For example, fluorination of 4-methoxynitrobenzene occurs very effectively to give high yields of the expected monofluorinated product and small quantities of the corresponding difluorinated derivative (Scheme 2). The solvents used were either acetonitrile or acetonitrile/formic acid mixtures, and the reactions were carried out at between 0 and 5 °C to minimise reaction between fluorine and the reaction solvent. All products were purified and isolated by column chromatography.

Fluorination of highly deactivated aromatic substrates in which electron-withdrawing groups are located at the 1 and 3-positions occurs effectively in flow processes.[26] Although

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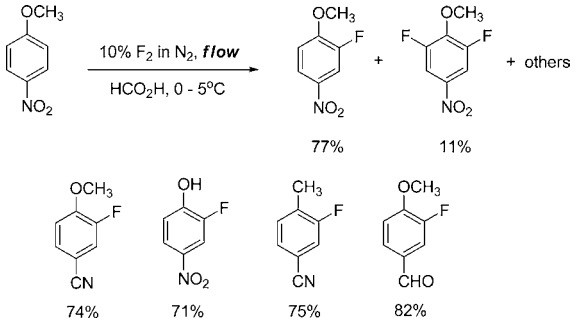
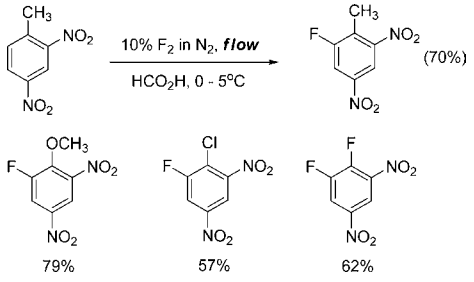
Scheme 2. Fluorination of 1,4-disubstituted aromatic derivatives



reactions are very slow, clean conversion to single products allows synthesis and isolation of corresponding 5-fluoroaromatic products by column chromatography (Scheme 3).

Scheme 3. Fluorination of 1,3-disubstituted aromatic derivatives

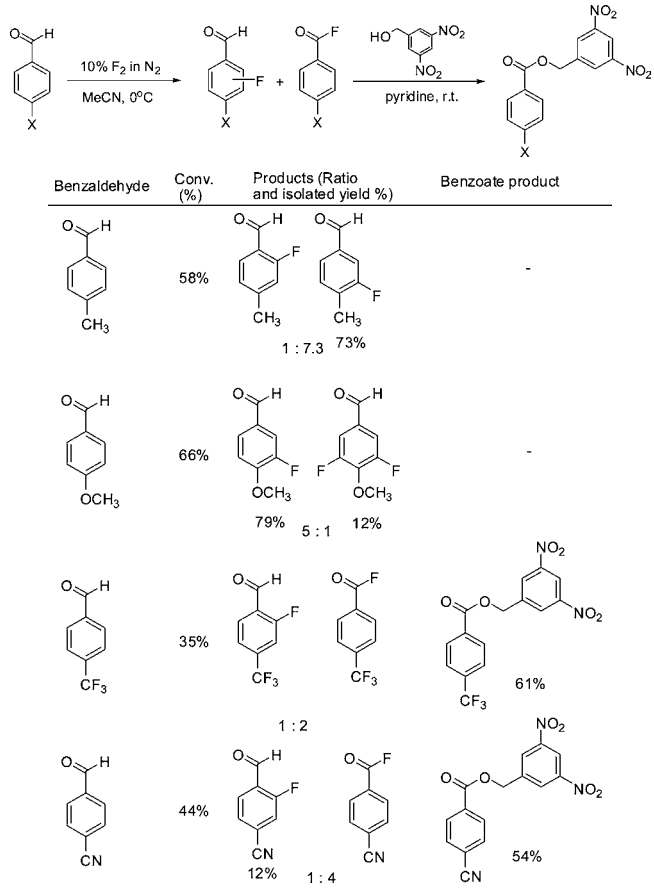


Direct fluorination of various benzaldehyde derivatives was studied, and the product profiles were dependent upon the substituent attached to the aromatic ring (Table 1).[27] Benzaldehyde substrates bearing electron-donating substituents such as methoxy groups gave products arising from ring fluorination because the aromatic ring is sufficiently activated towards electrophilic attack in this case. Conversely, benzaldehyde systems bearing electron-withdrawing substituents gave corresponding acid fluorides as the main products since, for these systems, the ring is too deactivated to compete with fluorination of the pendant aldehyde group. The acid fluoride derivatives were isolated as esters upon reaction of the crude product mixture with 3,5-dinitrobenzylalcohol (Table 1).

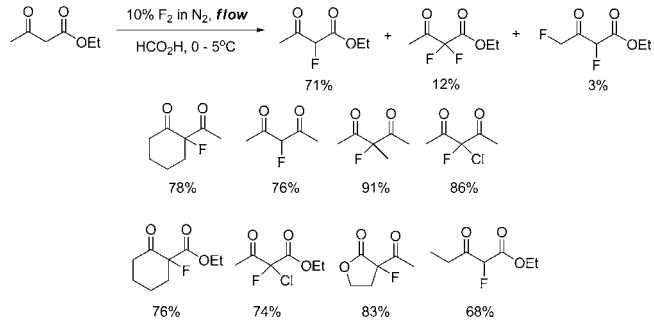
3.2. Fluorination of 1,3-Dicarbonyl Systems. In general, selective fluorination of 1,3-diketone and -ketoester systems proceeds very efficiently using continuous flow methodology,[23,28] and although some byproducts arising from polyfluorination occur in most cases, high isolated yields of the desired 2-fluoro-1,3-dicarbonyl systems are obtained (Scheme 4).

The polyfluorinated products can be readily washed from the crude product mixtures by water, leaving predominantly monofluorinated product of sufficient purity for further chemical transformation. Since it is practically very difficult to separate the 1,3-dicarbonyl substrate from the desired monofluorinated product, it is much more convenient to adjust the flow rates of substrate and fluorine to achieve complete conversion of substrate which, although this may lead to some difluorinated products formed even in a flow regime, enables a much more straightforward purification and isolation of the 2-fluoro-1,3-dicarbonyl product.

Table 1. Fluorination of benzaldehyde derivatives



Scheme 4. Fluorination of 1,3-diketone derivatives



Since fluorination of dicarbonyl substrates occurs by reaction of the corresponding enol systems, 1,3-dicarbonyl derivatives that have a high enol content at equilibrium and/or a very rapid rate of enolisation in the acetonitrile reaction medium, such as pentane-1,3-dione, are fluorinated very efficiently, and high yields of fluorinated product can be isolated. Conversely, 1,3-dicarbonyl substrates that have a low enol content at equilibrium and/or a slow enolisation rate gave lower yields of the fluorinated product under the reaction conditions employed. The rates of enolisation were too slow to be aided by longer residence times within the flow reactor channel, and so these substrates can be more difficult to fluorinate in either batch or flow procedures.

Fluorination of diethyl malonate gives a mixture of several byproducts arising from fluorination of the pendant ethyl groups which compete effectively with fluorination at the methylene site because of the low enol content of this system at

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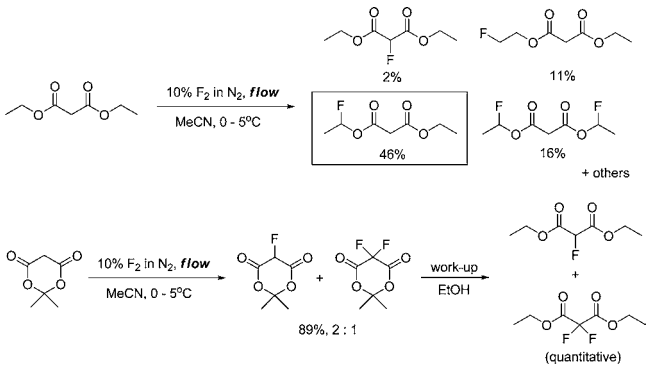
equilibrium in acetonitrile. Difficult purification of the product mixture makes this direct route for the synthesis of fluorodiethyl malonate not synthetically viable (Scheme 5).[29]

Scheme 5. Fluorination of 1,3-diester derivatives



However, fluorination of the related system, Meldrum's acid, gives the corresponding mono- and difluorinated systems[29] which are transformed to the 2-fluoromalonate derivative in high yield upon work-up in ethanol. Again, the difluorinated product could be separated from the desired monofluorinated system by an aqueous wash of the crude product mixture.

In recent studies, fluorination of diketone substrates and subsequent in situ cyclisation of the intermediate fluorodiketone by reaction with appropriate hydrazine derivatives, which is added to the reagent stream via a T-piece, in a two-step, sequential continuous flow process gave ready access to various 4-fluoropyrazole products (Figure 5).[30] Flow rates of fluorine

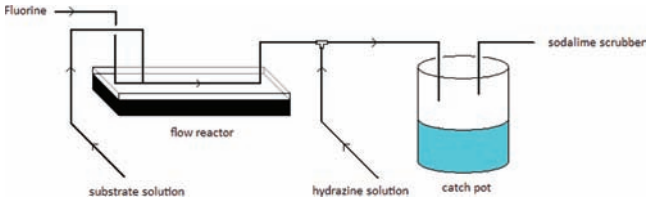


Figure 5. Flow reactor for sequential gas–liquid/liquid–liquid flow processes.

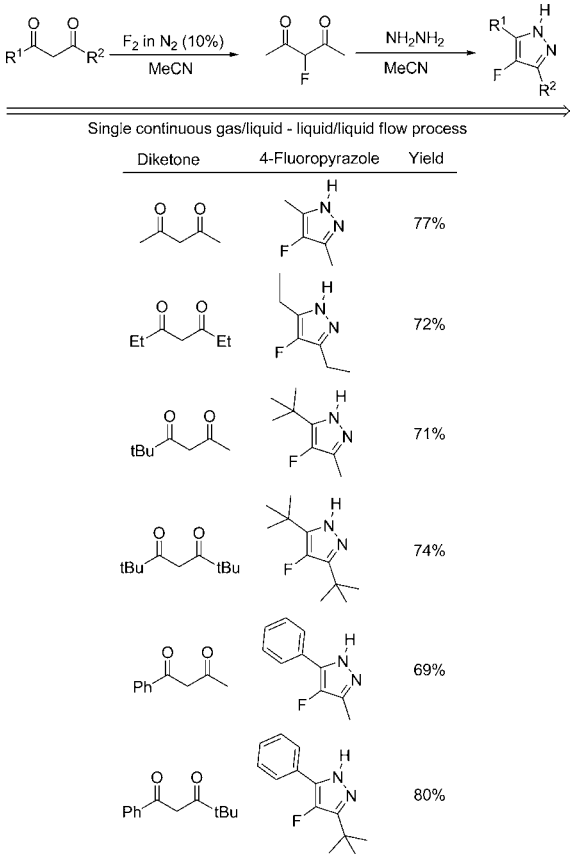
were adjusted so that complete conversion of the diketone is achieved in the first stage of the reaction sequence since any difluorinated product will not react further with the hydrazine system and can be easily separated from the fluoroheterocyclic product (Table 2).

4. OXIDATION REACTIONS USING FLUORINE

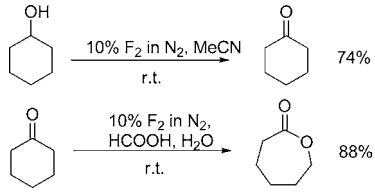
Elemental fluorine is, of course, a very strong oxidising agent and can be used to selectively oxidise secondary alcohols (Scheme 6) to the corresponding ketones in flow regimes.[31]

Reaction of fluorine with water in acetonitrile gives the very powerful electrophilic oxygen transfer agent, HOF·MeCN, which has been used previously in small-scale batch processes by Rozen and co-workers[32] to effect the oxidation of many alkenes, amines, sulfur-containing compounds, and heterocycles, for example, in very resource-efficient, rapid reactions that do not produce any toxic heavy metal waste. However, HOF·MeCN is relatively unstable at room temperature and has a half-life of around a few hours. The problems of adding substrates to highly concentrated oxidising media in terms of

Table 2. Synthesis of 4-fluoro-3,5-dimethylpyrazole derivatives



Scheme 6. Oxidation reactions using fluorine



reaction and temperature control are also in common with the problems involved with using many other oxidising systems such as hydrogen peroxide, peroxy acids, and heavy metal oxides.

Sequential formation and in situ reaction of HOF·MeCN in a flow reactor system (Figure 6) provide an effective, readily scalable methodology that makes use of the very high oxidative power of this reagent system and overcomes the problems of low reagent stability. With the use of the sequential flow reactor system a range of alkenes were very effectively epoxidised at room temperature[33] (Scheme 7) and amines transformed to corresponding nitro derivatives (Scheme 8).[34] By similar processes various aniline systems including some very electron-deficient aniline substrates were also very efficiently oxidised to the corresponding nitrobenzene systems (Scheme 9) in high isolated yields.[34]

5. CONCLUSIONS

Fluorine gas has been underutilized as a reagent for organic synthesis due to continuing perceptions regarding its uncontrollable and unselective reactivity. However, by using

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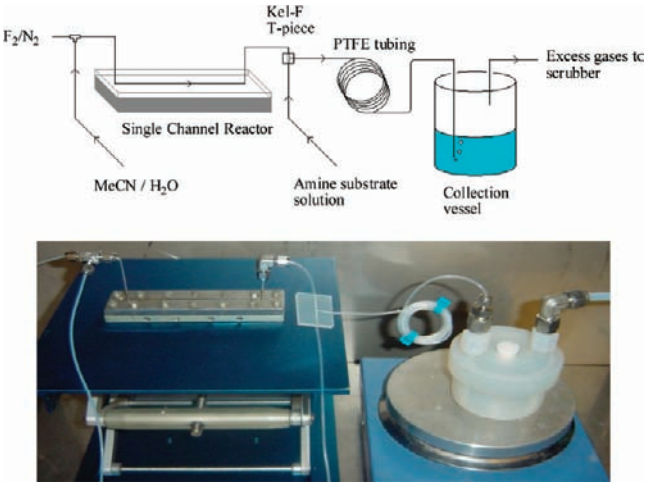
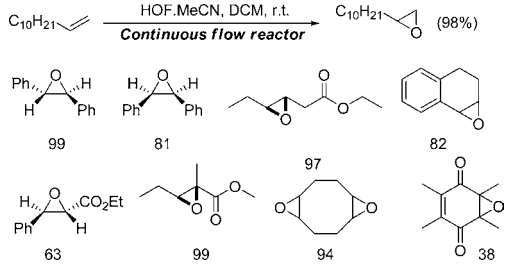
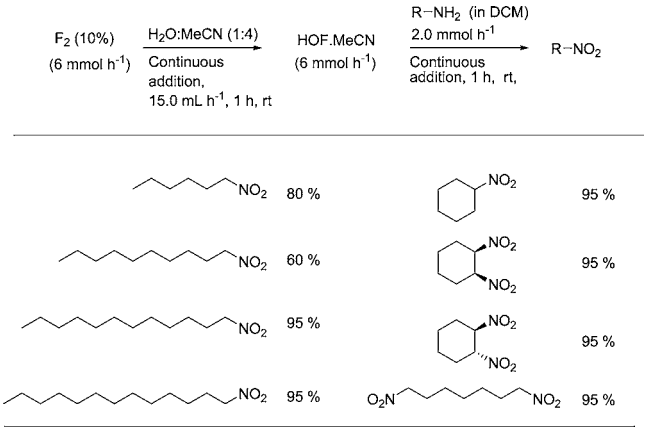


Figure 6. Flow reactor for generation and use of HOF·MeCN.

Scheme 7. Flow epoxidation using HOF·MeCN



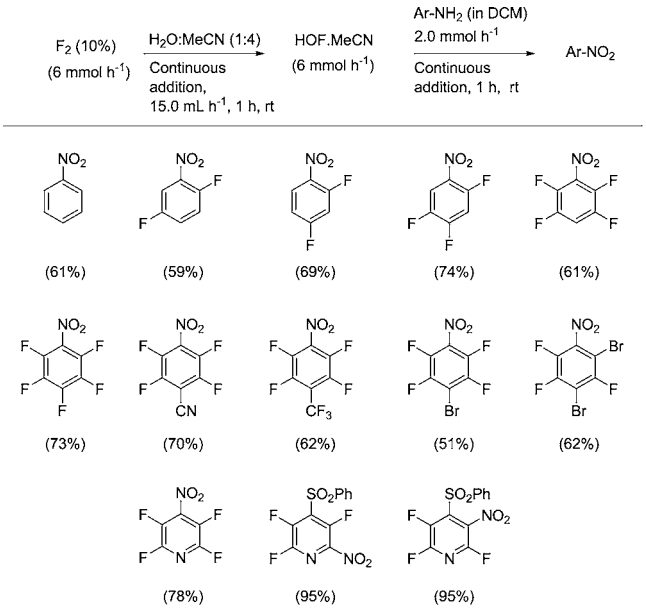
Scheme 8. Flow oxidation of amines using HOF·MeCN



an appropriate solvent system and temperature control in addition to flow chemistry techniques, fluorine gas may now be utilised as a selective, resource-efficient, fluorinating agent for a variety of direct fluorination processes. Fluorination of aromatic and dicarbonyl systems have all been carried out very successfully in flow systems, and recent multistep sequential syntheses involving direct fluorination as the first step of a reaction sequence indicate the potential use and versatility of flow fluorination processes. Furthermore, oxidation reactions involving the generation and in situ reaction of HOF·MeCN from fluorine gas now allow oxidation processes to be carried out in scalable flow regimes giving minimal waste streams using this very powerful oxygen transfer reagent.

Fluorine is less toxic than the widely used and accepted reagent chlorine and is commercially available in cylinders as

Scheme 9. Oxidation of aromatic amines using HOF·MeCN



prediluted mixtures in nitrogen. With the advent of gas–liquid flow reactors that may be used to further control fluorination and oxidation processes, synthetic chemists should now consider adding fluorine gas to their range of reagents that are regularly in use in the laboratory. In particular, given the low cost of fluorine, development chemists should certainly regard fluorine as a useful reagent in the development phases of new fluorinated chemical intermediates.

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Notes

The authors declare no competing financial interest.

REFERENCES

(1) Gadamasetti, K. G. *Process Chemistry in the Pharmaceutical Industry*; Marcel Dekker: New York, 1999.

(2) Ehrfeld, W.; Hessel, V.; Lowe, H. *Microreactors. New Technology for Modern Chemistry*; Wiley-VCH: New York, 2000.

(3) Wiles, C.; Watts, P. *Microreaction Technology in Organic Synthesis*; CRC Press: Boca Raton, 2011.

(4) For examples of commercially available reactor systems for continuous flow processes see the following: www.asynt.com, www.thalesnano.com, www.chemtrix.com, and www.syrris.com.

(5) Valera, F. E.; Quaranta, M.; Moran, A.; Blacker, J.; Armstring, A.; Cabral, J. T.; Blackmond, D. G. *Angew. Chem., Int. Ed.* **2010**, *49*, 2478–2485.

(6) Chambers, R. D. *Fluorine in Organic Chemistry*; Blackwell: Oxford, 2004.

(7) Uneyama, K. *Organofluorine Chemistry*; Blackwell: Oxford, 2006.

(8) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; John Wiley and Sons: New York, 1991.

(9) Baasner, B.; Hagemann, H.; Tatlow, J. C. *Houben-Weyl Organofluorine Compounds*; Thieme: Stuttgart, 2000; Vol. *E10a*.

(10) Banks, R. E.; Smart, B. E.; Tatlow, J. C. *Organofluorine Chemistry. Principles and Commercial Applications*; Plenum: New York, 1994.

(11) Baumann, M.; Baxendale, I. R.; Ley, S. V. *Synlett* **2008**, 2111–2114.

(12) Baumann, M.; Baxendale, I. R.; Martin, L. J.; Ley, S. V. *Tetrahedron* **2009**, *65*, 2111−2114.
(13) Gustafsson, T.; Gilmour, R.; Seeberger, P. H. *Chem. Commun.* **2008**, 3022−3024.
(14) Lagow, R. J.; Margrave, J. L. *Prog. Inorg. Chem.* **1979**, *26*, 161−210.
(15) Purrington, S. T.; Kagen, B. S.; Patrick, T. B. *Chem. Rev.* **1986**, *86*, 997−1018.
(16) Hutchinson, J.; Sandford, G. *Top. Curr. Chem.* **1997**, *193*, 1−43.
(17) Butters, M.; Ebbs, J.; Green, S. P.; MacRae, J.; Morland, M. C.; Murtiashaw, C. W.; Pettman, A. J. *Org. Process Res. Dev.* **2001**, *5*, 28−36.
(18) Jahnisch, K.; Baerns, M.; Hessel, V.; Ehrfeld, W.; Haverkamp, V.; Lowe, H.; Wille, C.; Guber, A. *J. Fluorine Chem.* **2000**, *105*, 117−128.
(19) Dingerdissen, U.; Janisch, K. *Chem. Eng. Technol.* **2005**, *28*, 426−427.
(20) Ehrich, H.; Linke, D.; Morgenschweis, K.; Baerns, M.; Janisch, K. *Chimia* **2002**, *56*, 647−653.
(21) Chambers, R. D.; Spink, R. C. H. *Chem. Commun.* **1999**, 883−884.
(22) Chambers, R. D.; Holling, D.; Sandford, G.; Spink, R. C. H. *Lab Chip* **2001**, *1*, 132−137.
(23) Chambers, R. D.; Fox, M. A.; Holling, D.; Nakano, T.; Okazoe, T.; Sandford, G. *Lab Chip* **2005**, *5*, 191−198.
(24) De Mas, N.; Gunther, A.; Schmidt, M. A.; Jensen, K. F. *Ind. Eng. Chem. Res.* **2003**, *42*, 698−710.
(25) Chambers, R. D.; Hutchinson, J.; Sparrowhawk, M. E.; Sandford, G.; Moilliet, J. S.; Thomson, J. *J. Fluorine Chem.* **2000**, *102*, 169−173.
(26) Chambers, R. D.; Fox, M. A.; Sandford, G.; Trmcic, J.; Goeta, A. *J. Fluorine Chem.* **2007**, *28*, 29−33.
(27) Chambers, R. D.; Sandford, G.; Trmcic, J.; Okazoe, T. *Org. Process Res. Dev.* **2008**, *12*, 339−244.
(28) Chambers, R. D.; Fox, M. A.; Sandford, G. *Lab Chip* **2005**, *5*, 1132−1139.
(29) Chambers, R. D.; Fox, M. A.; Holling, D.; Nakano, T.; Okazoe, T.; Sandford, G. *Chem. Eng. Technol.* **2005**, *28*, 344−352.
(30) Breen, J. R.; Sandford, G.; Yufit, D. S.; Howard, J. A. K.; Fray, J.; Patel, B. *Beilstein J. Org. Chem.* **2011**, *7*, 1048−1054.
(31) Chambers, R. D.; Holling, D.; Rees, A. J.; Sandford, G. *J. Fluorine Chem.* **2003**, *119*, 81−82.
(32) Rozen, S. *Eur. J. Org. Chem.* **2005**, *12*, 2433−2447.
(33) McPake, C. B.; Murray, C. B.; Sandford, G. *Tetrahedron Lett.* **2009**, *50*, 1674−1676.
(34) McPake, C. B.; Murray, C. B.; Sandford, G. *ChemSusChem* **2012**, *5*, 312−319.