Graham Sandford
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Continuous flow reactors for gas/liquid chemical processes

Flow Chemistry Projects : 1995 - present

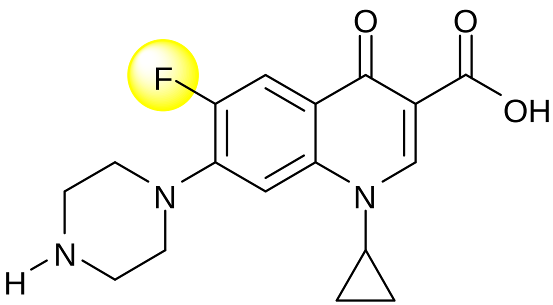
Durham	**Funding**
Rob Spink	BNFL
Darren Holling	DU Quota
Jelena Trmcic	Asahi Glass Co. (Japan)
Takashi Nakano	Asahi Glass Co. (Japan)
Mark Fox	Crystal Faraday / EPSRC Partnership
Chris McPake	AWE CASE
Jess Breen	Pfizer CASE

Prof. Richard D. Chambers

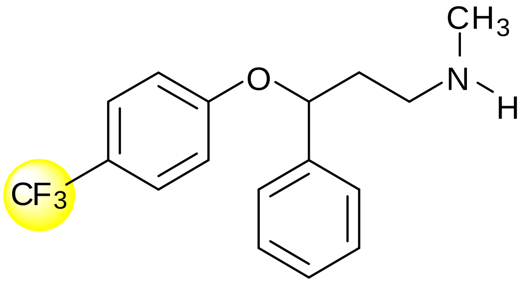
Organofluorine Chemistry

Fluorine may effect physiological properties of molecules

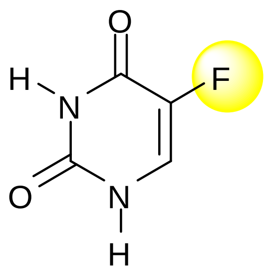
Commercially very valuable for life-science products



Ciprofloxacin (Bayer)



Prozac (Eli Lilley)

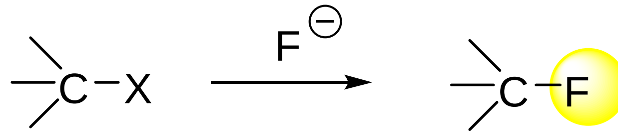


5-FU (anti-cancer)

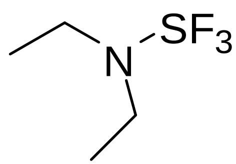
How do we introduce fluorine into organic systems ?

Carbon-Fluorine bond formation

Nucleophilic Fluorinating agents

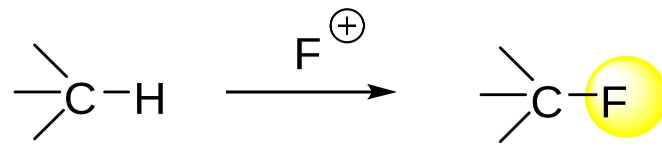


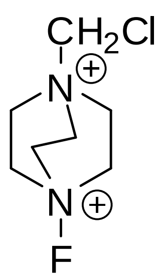
X = leaving group

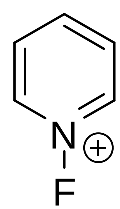
HF 

KF Et_4NF $Et_3N.3HF$ etc.

Electrophilic fluorinating agents



F_2 

2 $BF_4^{\ominus}$ 

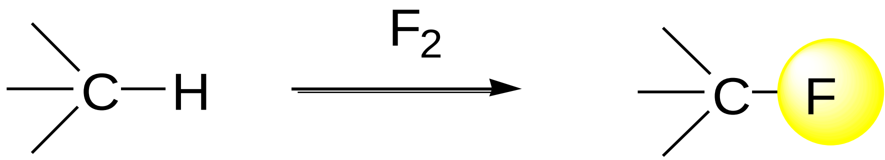
$BF_4^{\ominus}$ etc.

For large scale low-cost manufacture HF KF F_2

Selective Direct Fluorination – Use of F_2

F_2 is now a viable reagent for synthetic organic chemistry

Replacement of Hydrogen by Fluorine

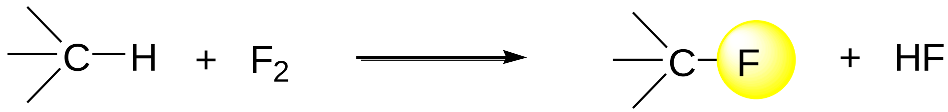


Reviews

- S.T. Purrington and B.S. Kagen, *Chem Rev.*, 1986, **86**, 997.
- R.J. Lagow and J.L. Margrave, *Prog. Inorg Chem.*, 1979, **26**, 161.
- J. Hutchinson and G. Sandford, *Top. Curr. Chem.*, 1997, **193**, 1.
- G. Sandford, *J. Fluorine Chem.*, 2007, **128**, 90.

Problems with using F_2

Heat of Reaction



$\Delta H = - 430\ kJmol^{-1}$

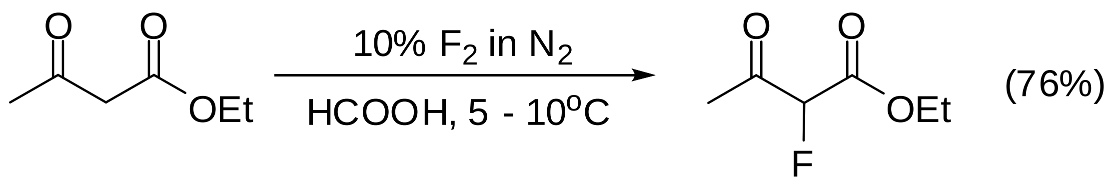
Require : efficient cooling
dilute F_2 in N_2
polar (MeCN) or acidic (HCOOH) reaction media

Possibility of aerosol formation

Safety on a large scale ?

Selective direct fluorination – batch process

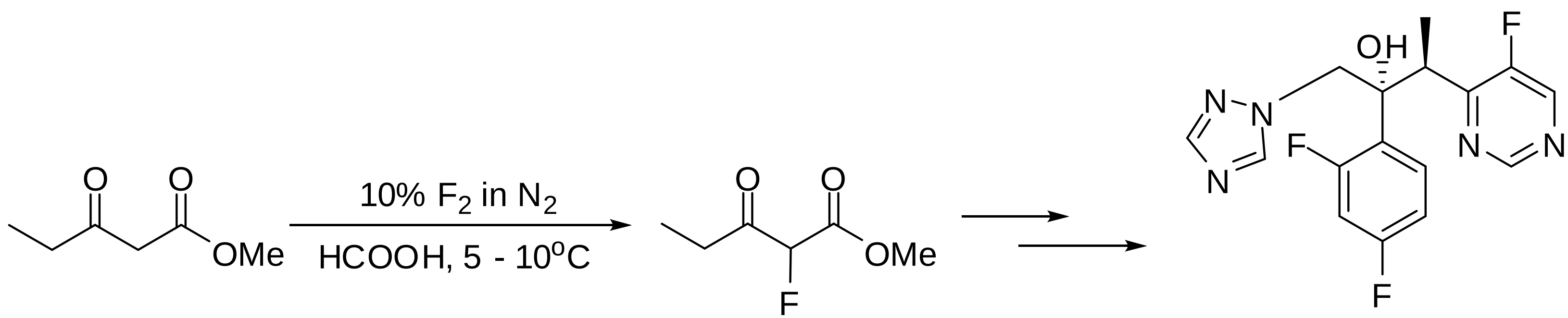
Direct fluorination of β-ketoesters first carried out at Durham on 1 g scale



Tetrahedron, 1996, **52**, 1

Industrial Application

Scale-up to 100s kg within 5 years for pharmaceutical production



Voriconazole
anti-fungal agent
Pfizer

Pfizer, *OPRD*, 2001, **5**, 28

Adapt to a continuous flow process on the industrial scale ??

Flow reactors for Direct Fluorination

Potential advantages:

Low inventories of F_2 in contact with reagents gives increased safety

Efficient mixing across phase boundary (gas/liquid)

More efficient heat exchange

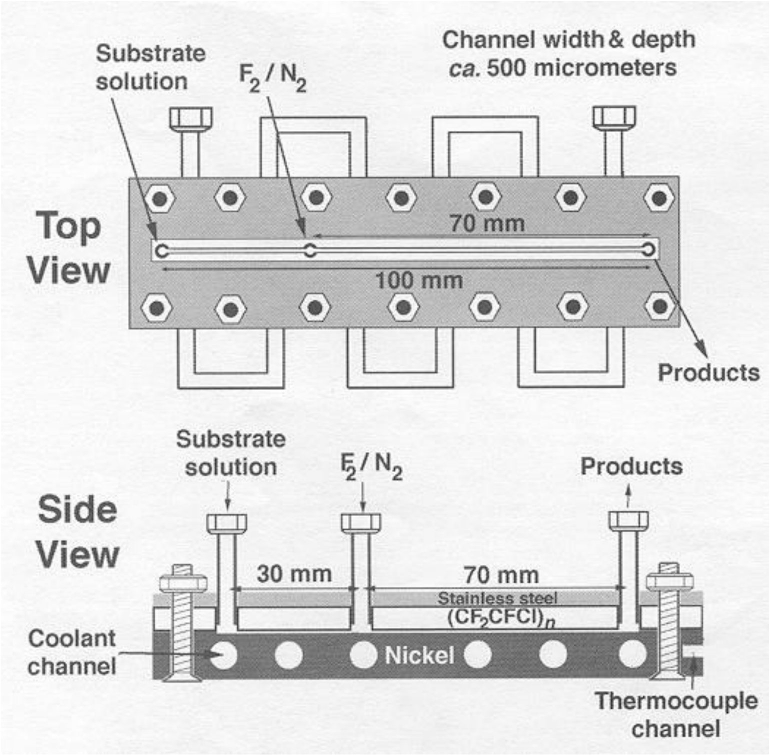
Large surface/volume ratio gives excellent gas/liquid interface

'Scale-out' rather than scale up

Good manufacturing practice (GMP) – lab. conditions are the same as the commercial plant

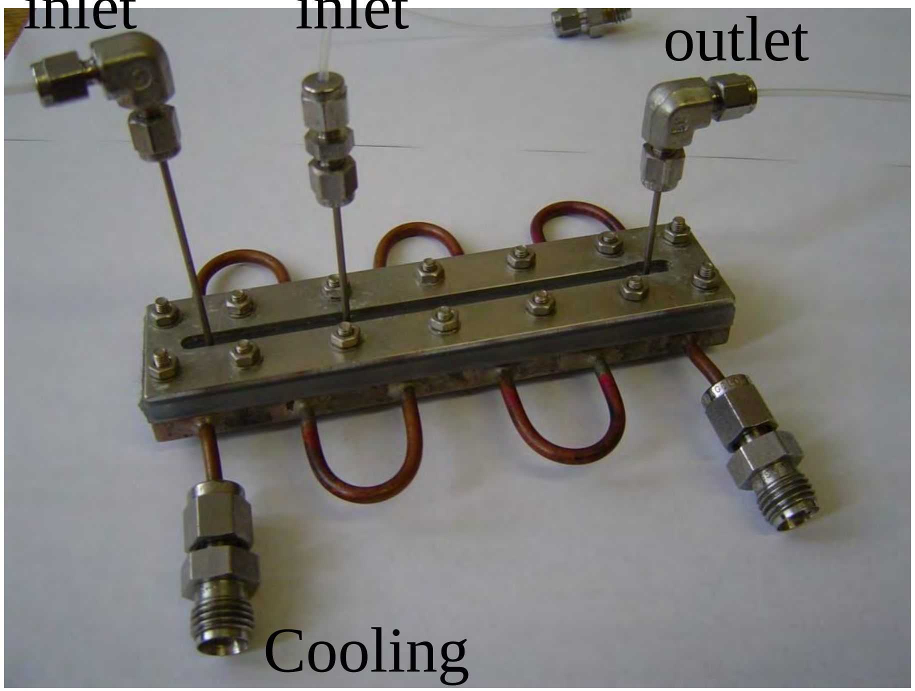
Single Channel Gas/Liquid Flow reactor

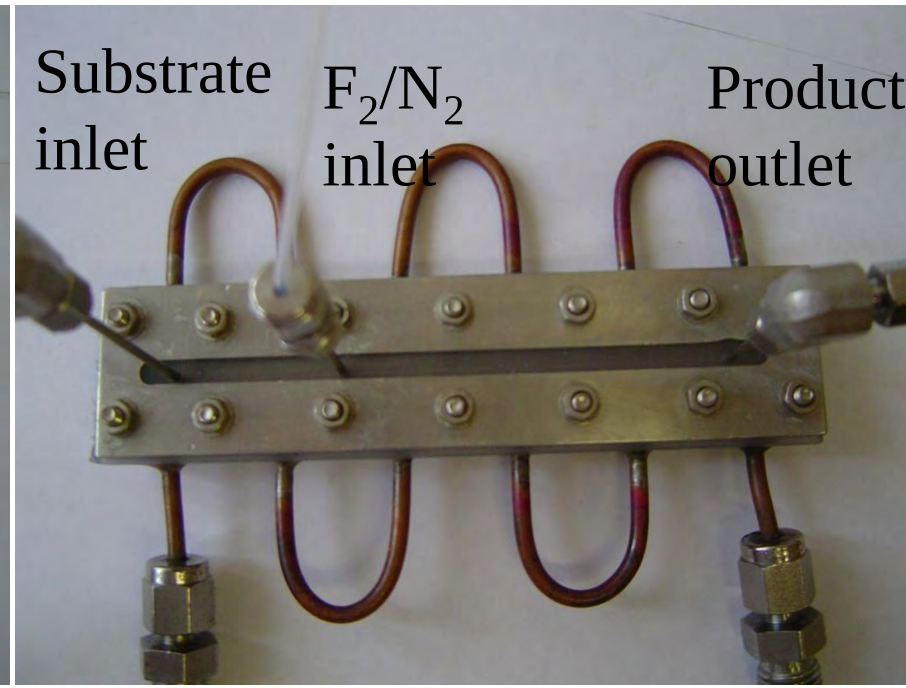
- Single groove cut into the surface of a nickel block (0.5 mm wide; 10 cm long)
- Kel-F viewing window
- Top-plate
- Reagents introduced via tubes cut through viewing plate
- Coolant channels through nickel block



Chem. Commun., 1999, 883

Single Channel Gas/Liquid Flow reactor

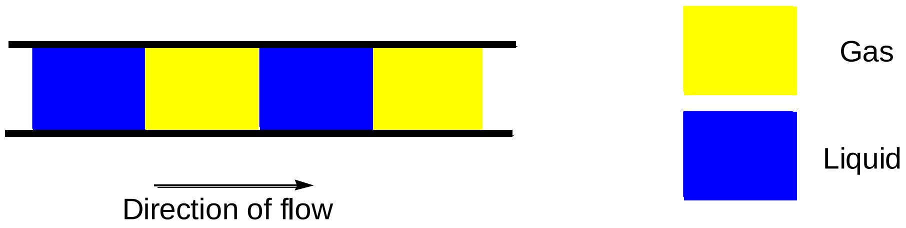




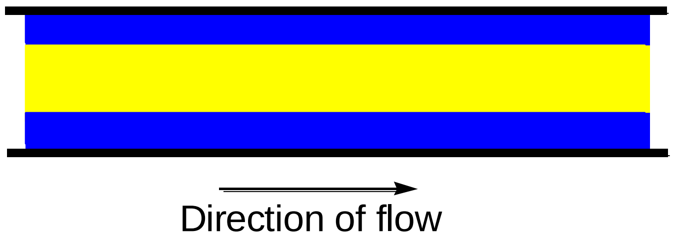
Chem. Commun., 1999, 883

Gas/Liquid 'pipe flow'

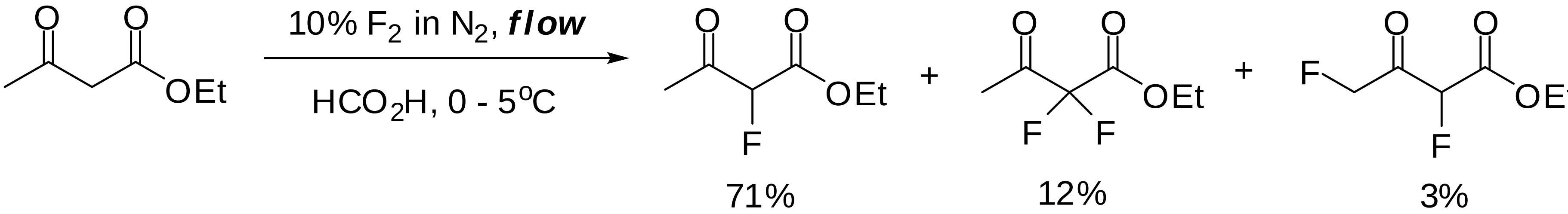
- 'Plug flow' not observed



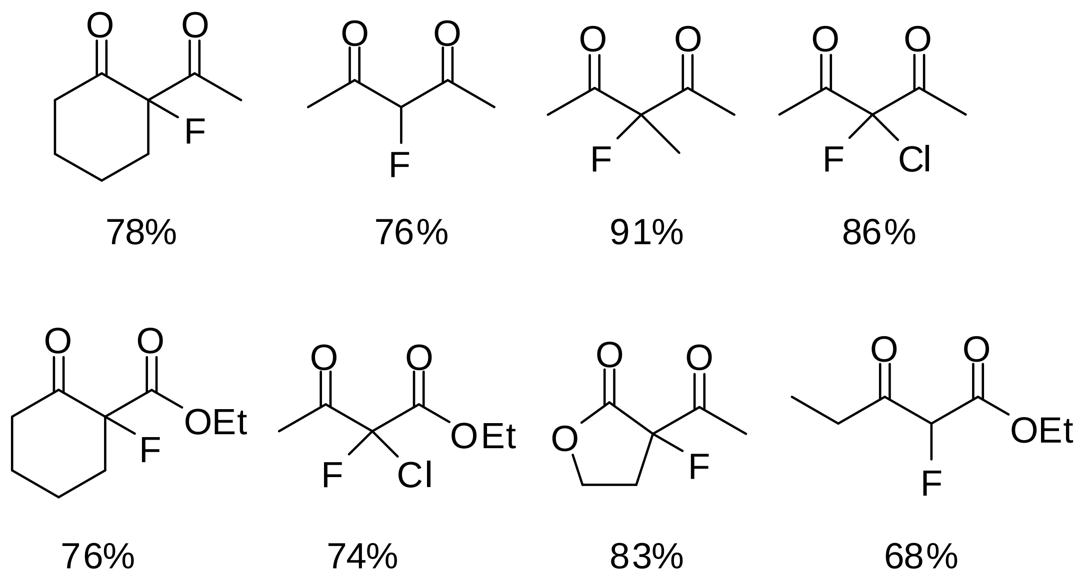
- 'Pipe flow' permits maximum phase interface



Selective fluorination – 1,3-Dicarbonyls



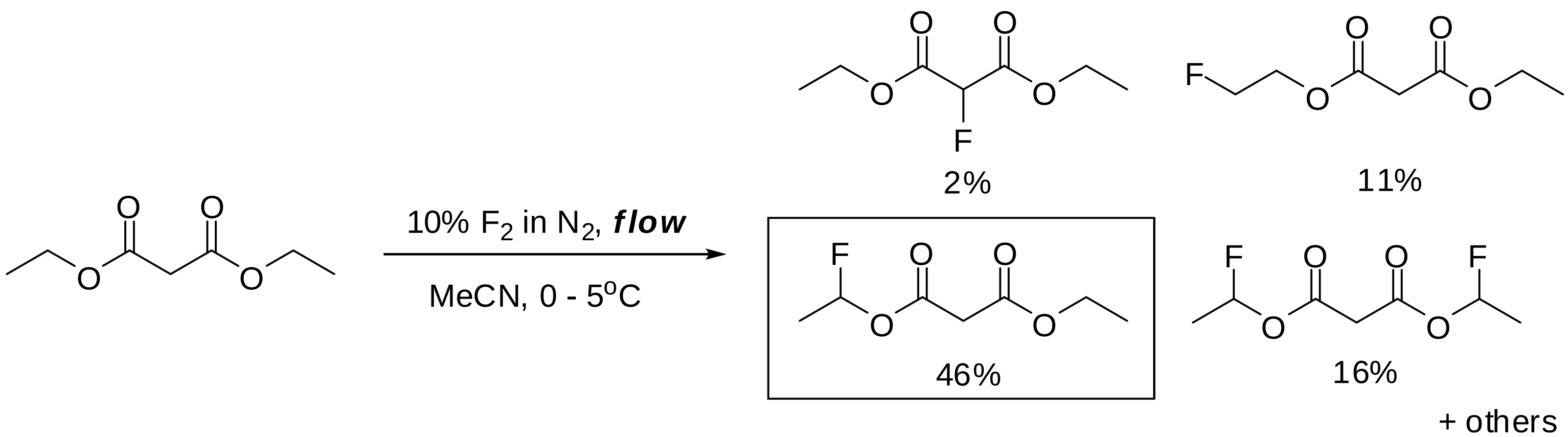
Difluorination observed but mono-fluorinated product separated and purified



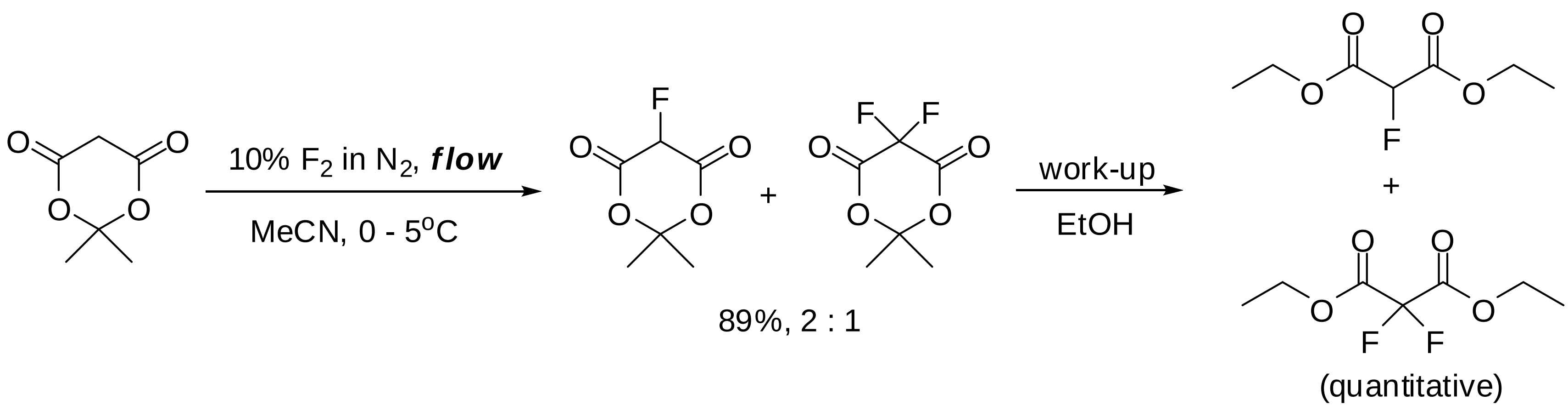
Lab. Chip, 2001, **1**, 132; *Lab Chip*, 2005, **5**, 1132

Selective fluorination – 1,3-Dicarbonyls

Fluorination of diethyl malonate gives mixtures



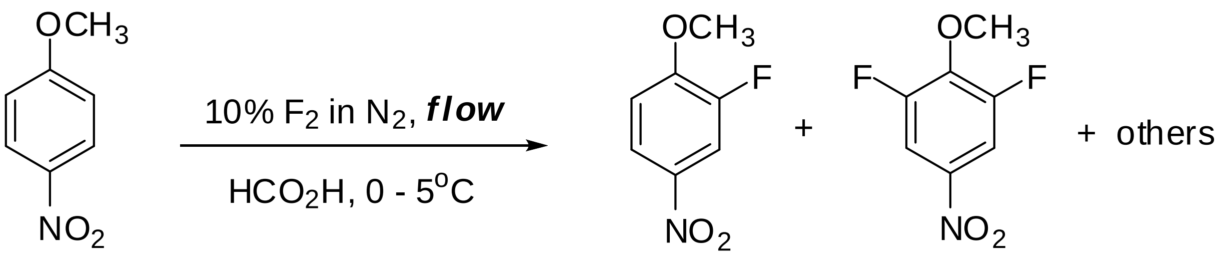
Meldrum’s acid preferred



Chem. Eng. Tech, 2005, **28**, 344

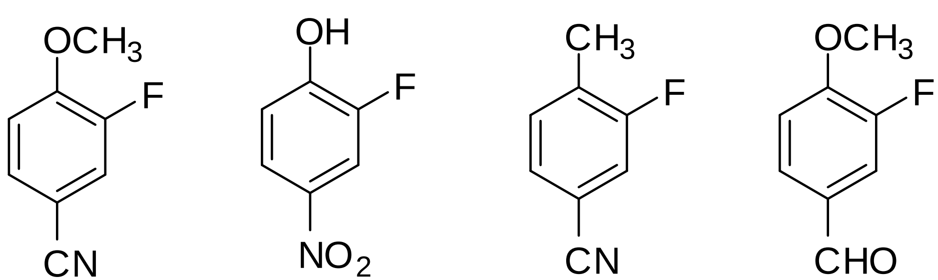
Selective fluorination - Aromatics

1,4-Disubstituted aromatic systems



77%   11%

Mono-fluorinated product separated and purified



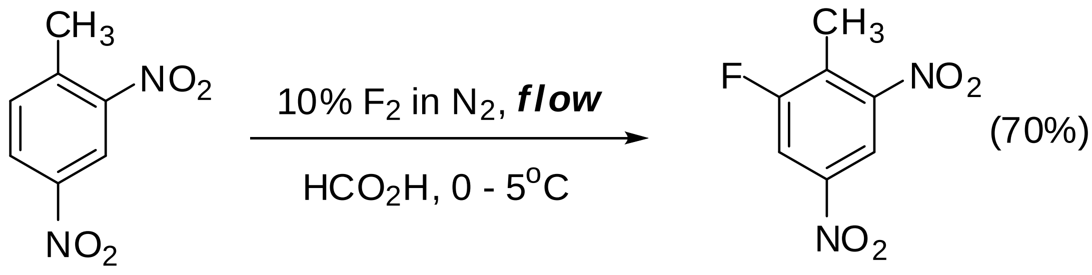
74%   71%   75%   82%

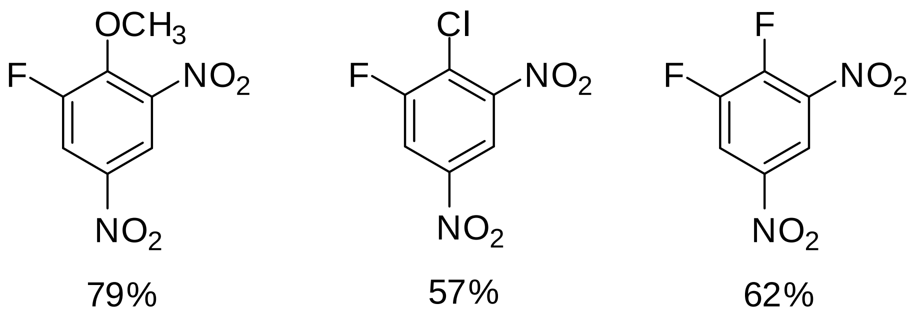
Alternative to multi-step Balz-Schiemann processes

Lab. Chip, 2001, **1**, 132

Selective fluorination - Aromatics

Deactivated 1,3-disubstituted aromatic systems

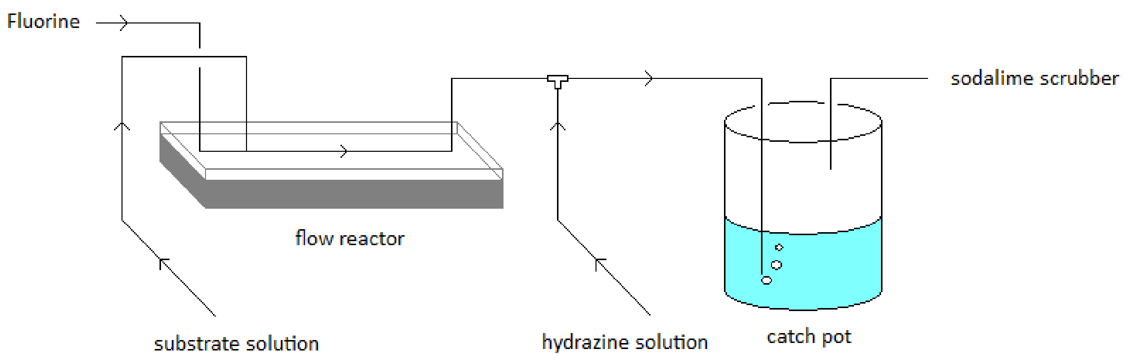


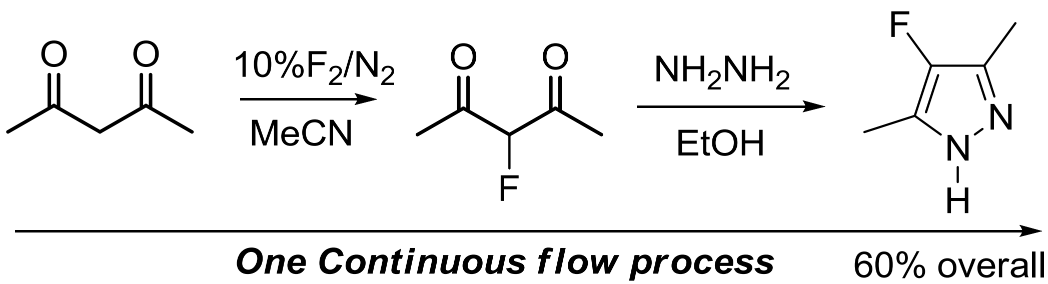


J. Fluorine Chem, 2007, **28**, 29

Gas/liquid – liquid/liquid processes

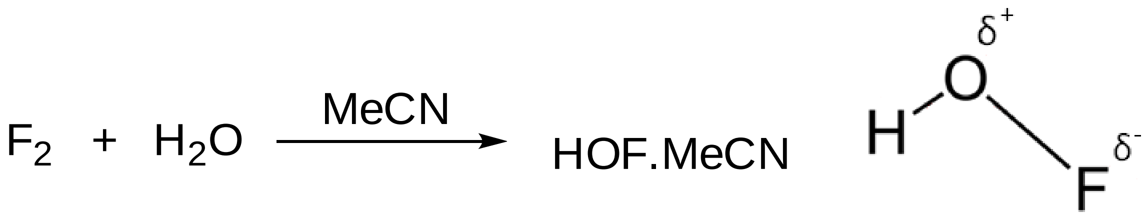
Sequential fluorination-cyclisation for fluoropyrazole formation





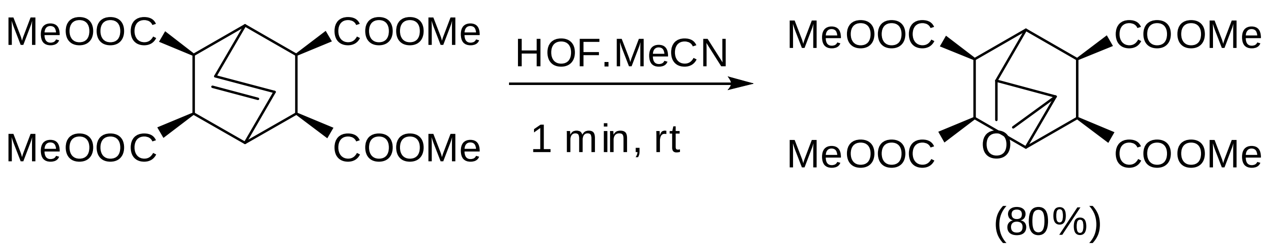
Gas/liquid Oxidation using HOF

F_2 can be used to 'enable' other difficult transformations such as oxidation processes



HOF.MeCN complex half life of ~3 h at rt
Extremely powerful oxygen transfer agent
Many oxidation reactions possible
No heavy metal by-products

S. Rozen, *J. Org. Chem.*, **1992**, 57, 7342
S. Rozen, *Eur. J. Org. Chem.* **2005**, 2433

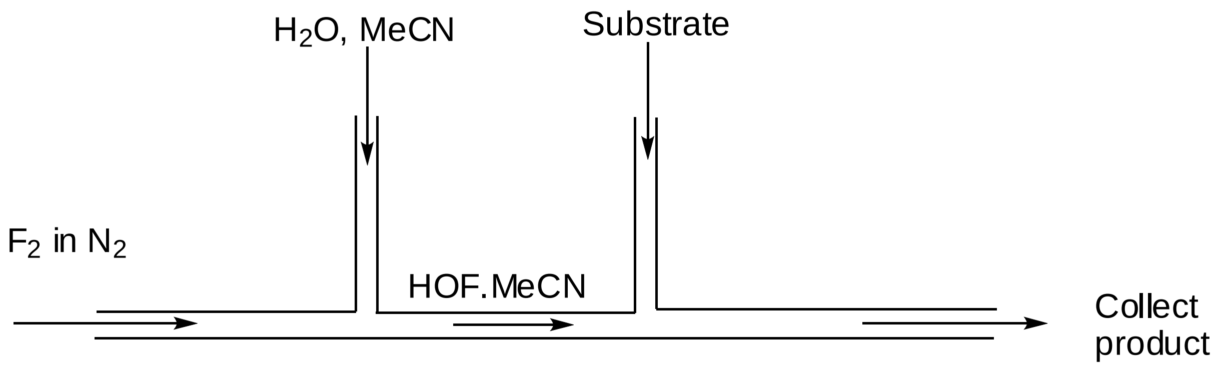


No reaction using DMDO or H_2O_2

Difficult to scale up in batch processes due to instability

Gas/liquid Oxidation using HOF

Can we synthesise and use HOF.MeCN in one continuous flow process ?

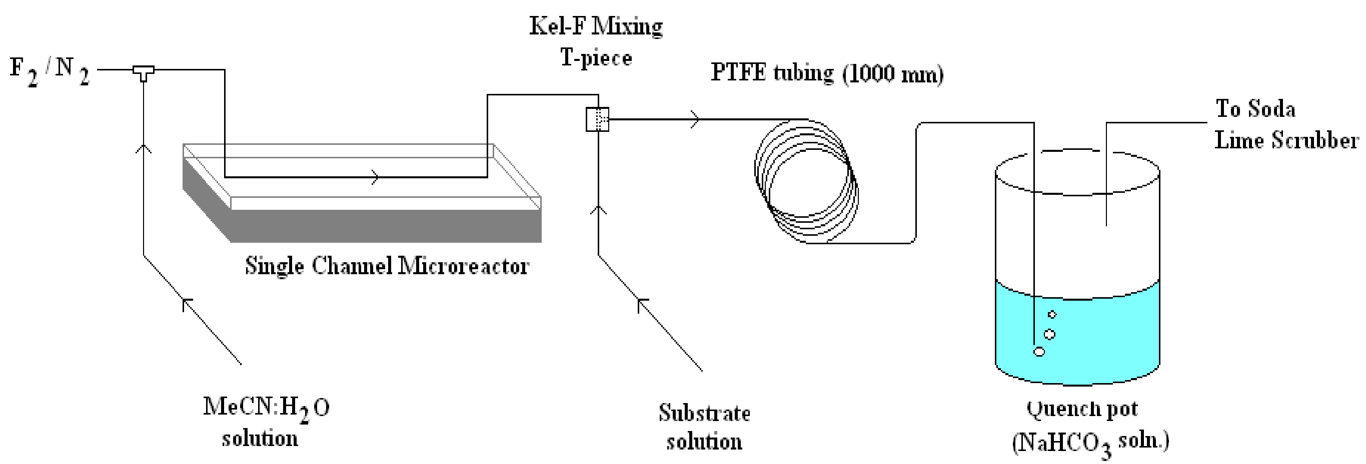


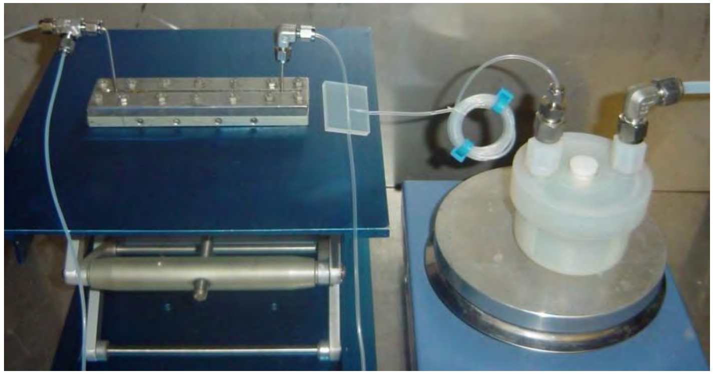
Gas/liquid – liquid/liquid sequential flow reaction

Low inventory of HOF.MeCN : Safer process

Gas/liquid Oxidation using HOF

Continuous flow oxidation using *in situ* generated HOF.MeCN



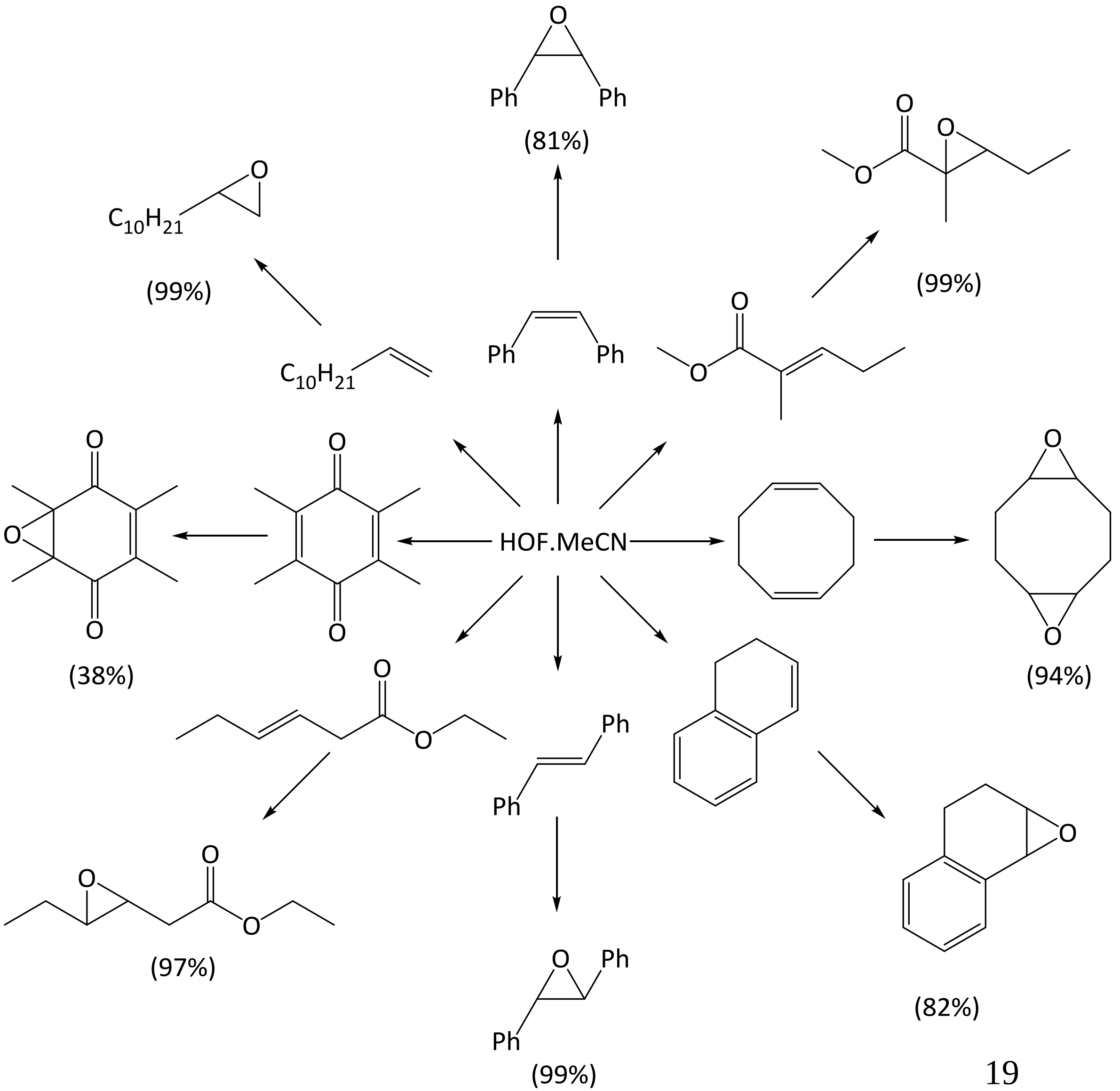


Applicable to large scale synthesis using continuous flow techniques

Gas/liquid Oxidation using HOF

Conditions

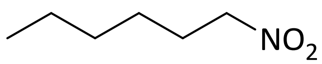
- Alkene - 2.0 mmol h^{-1}
- HOF.MeCN - 2.0 mmol h^{-1}
- Run time - 60 mins @ rt
- Reaction path length - 30 cm
- Yields calculated using ^{1}H NMR



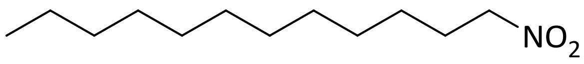
Tetrahedron Lett., **2009**, 50, 1674

Gas/liquid Oxidation using HOF

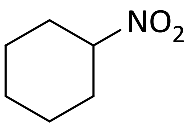
$$F_2\ (10\%) \xrightarrow[\text{Continuous addition, rt}]{H_2O:MeCN\ (1:4)} \text{HOF.MeCN}\ (6.0\ \text{mmol h}^{-1}) \xrightarrow[\text{Continuous addition, 30 mins, 1.0 or 2.0 mmol h}^{-1}\text{, rt}]{\text{Amine}} \text{Nitro alkane}$$



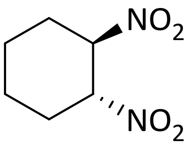
80%



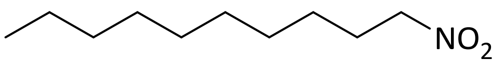
95%



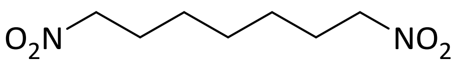
95%



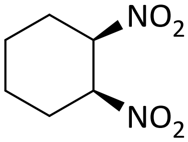
95%



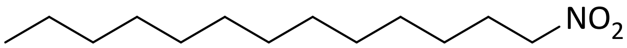
70%



95%



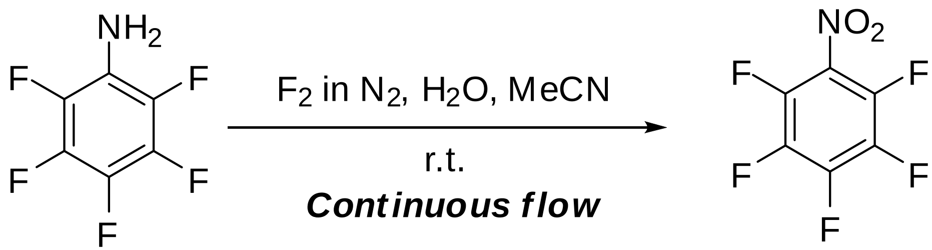
95%



95%

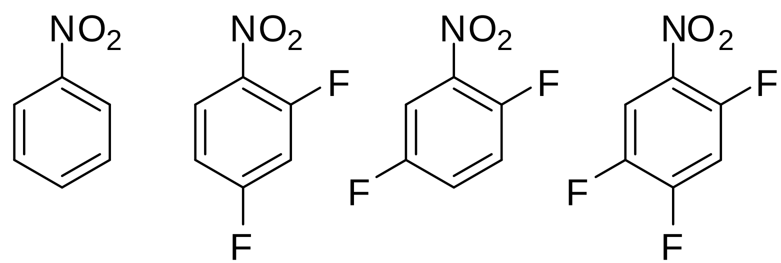
Chim. Oggi. **2010**, 28, 3

Gas/liquid Oxidation using HOF

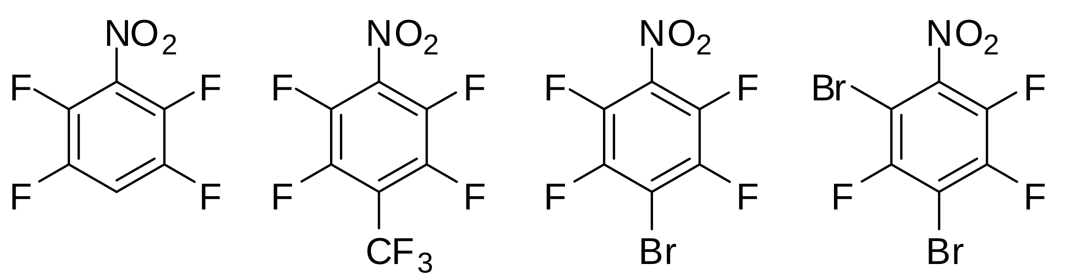


73%

Flow rates:
10% F_2 in N_2 (4.8 mmol h^{-1})
H_2O in MeCN (166 mmol h^{-1})
amine (2.0 mmol h^{-1})

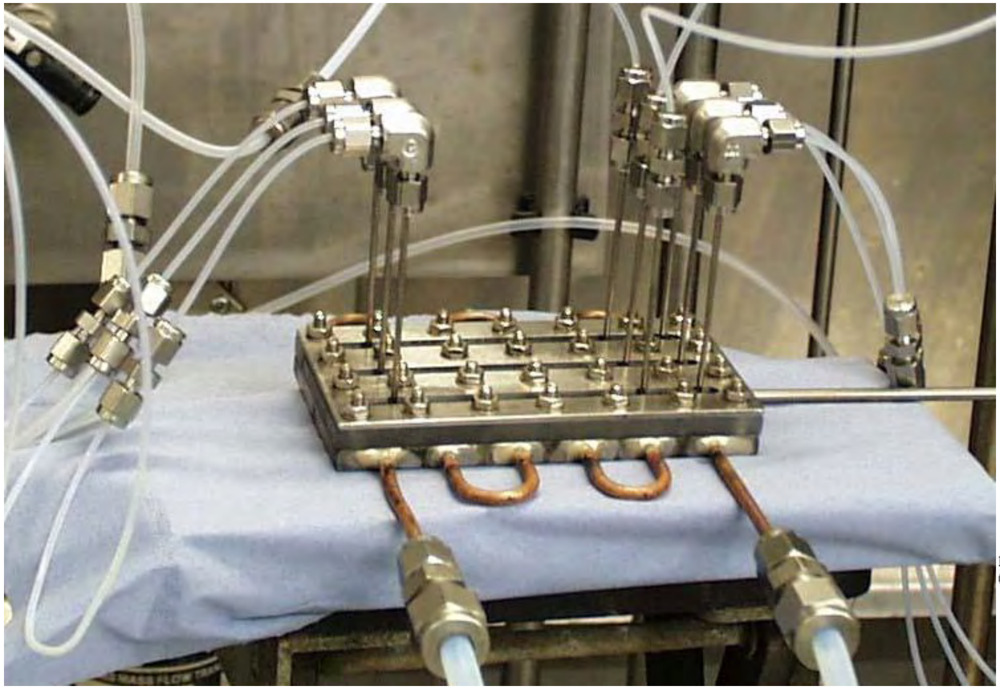


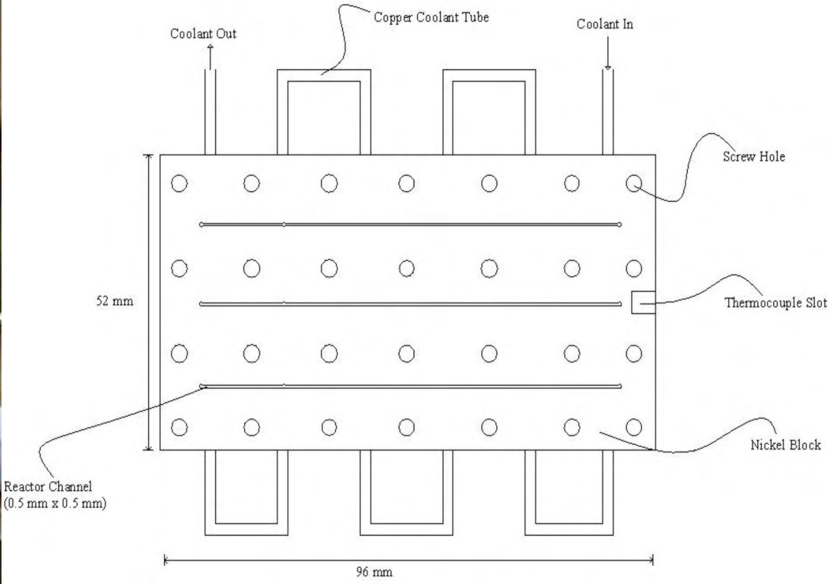
61% 61% 59% 74%



61% 40% 62% 51%

Scale-out to 3-channels





- A nickel plate with three grooves/channels etched into the surface
- Viewing and top plates

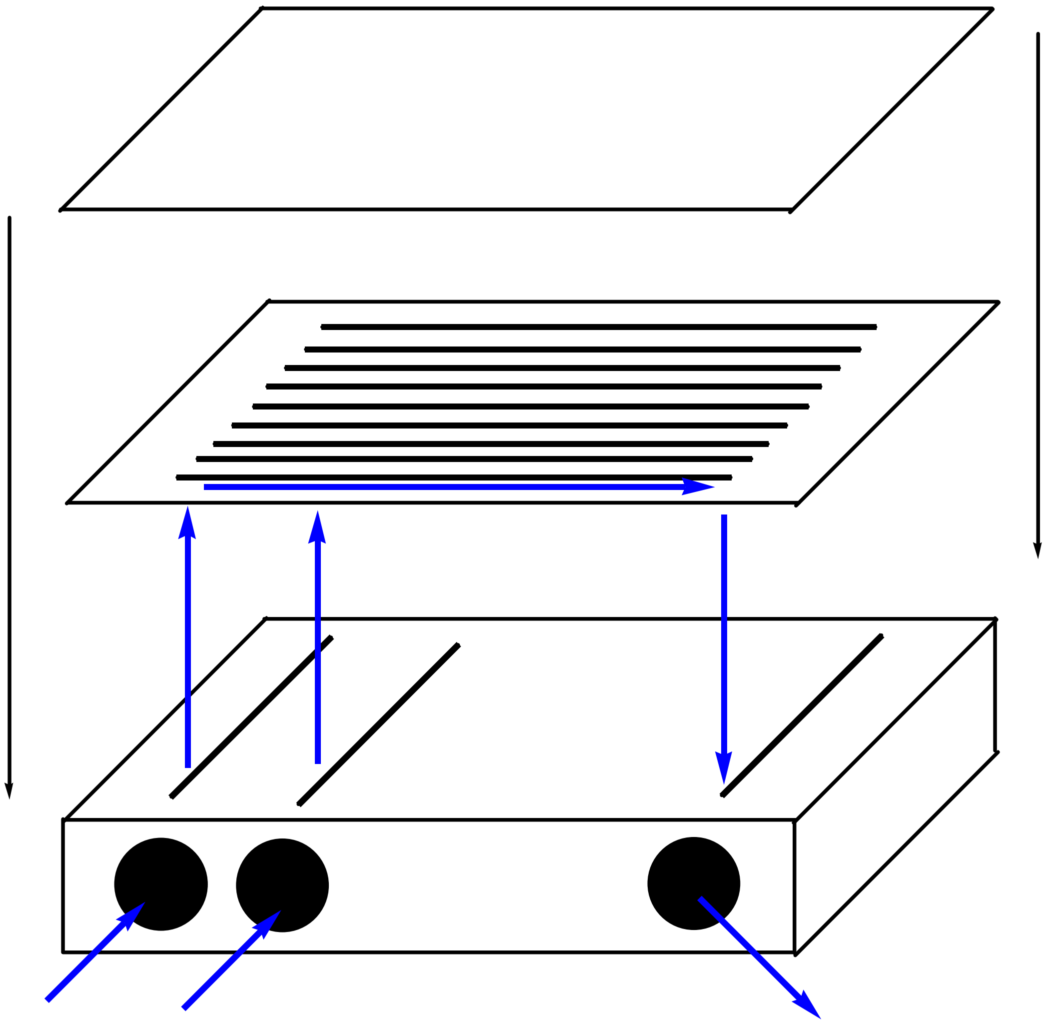
Lab Chip, 2001, **1**, 132

Scale-out challenges

- Difficult integration of microchannels supplied from one feed-stock
- No pre-cooling of gas or liquid substrates
- Uniform supply of feedstocks to channels
- Simple design for daily production and maintenance

Multi-channel reactor concept

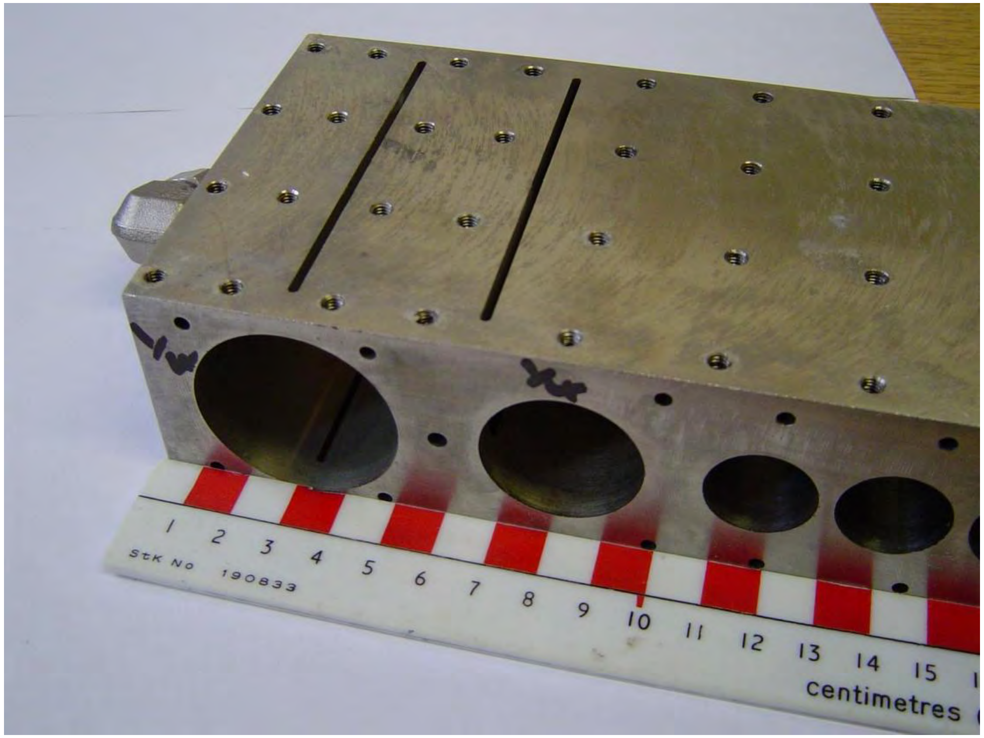
Durham University



Lab. Chip, 2005, **5**, 191

Multi-channel reactor – base block

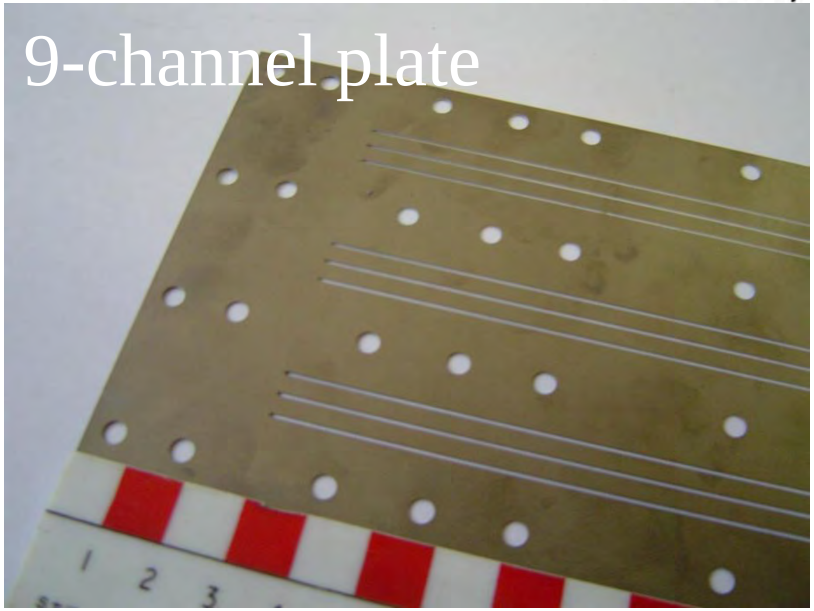
- Machined Stainless steel
- 3 reservoirs for substrates and product collection
- Slits leading from reservoirs to top of the plate
- Screw and cooling channel fittings

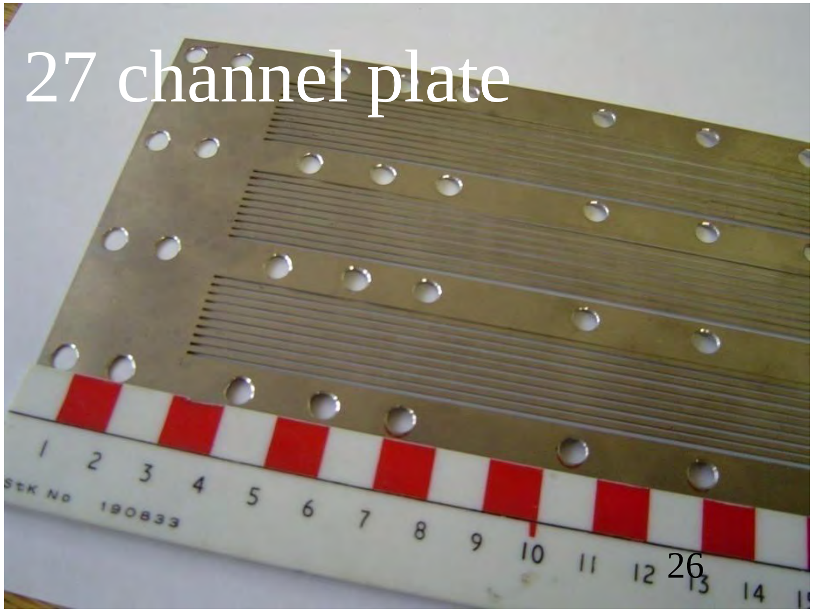


Multi-channel reactor – channel plates

Durham University

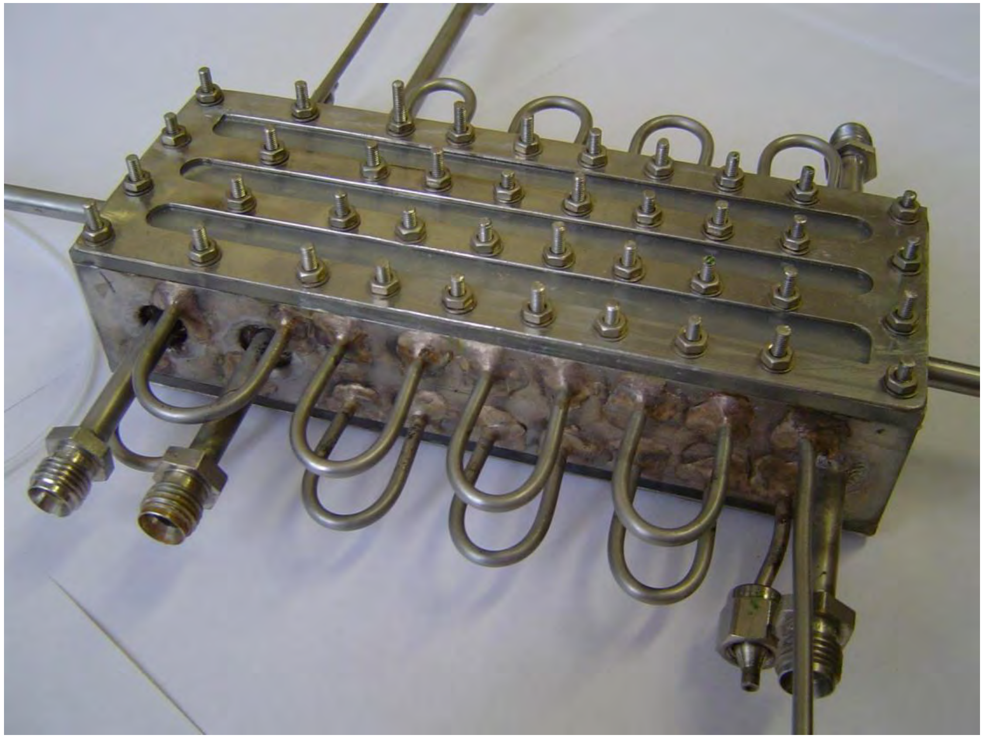
- 0.5 mm thick stainless steel
- 0.5 mm wide channels
- Number of channels per plate as required
- Fitted with crew holes to attach to base block





Multi-channel reactor – Final design

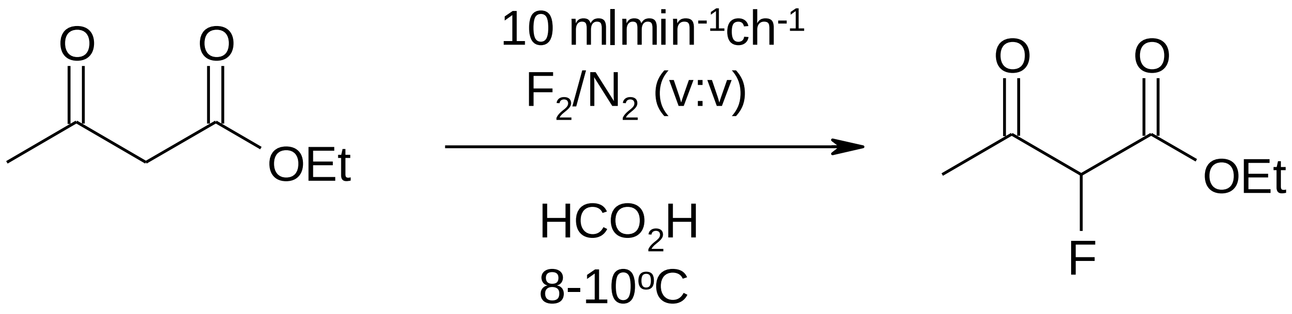
- External cooling of stainless steel block
- Sealing gaskets
- Various multi-channel plates (3, 9, 27 channels)
- Kel-F sealing plate for observation
- Mounted vertically



Multi-channel reactor - operation

Lab. Chip, 2005, **5**, 191

Multi-channel reactor – fluorination



0.5 $mlh^{-1}ch^{-1}$ (1.8 $mmolh^{-1}ch^{-1}$)

16.2 $mmolh^{-1}$ (2.11gh^{-1})

10% F_2 in N_2	83% conv.	87% yield
20% F_2 in N_2	93% conv.	94% yield

- Approx. 2 g product per channel per hour

Lab. Chip, 2005, **5**, 191

Multi-channel reactor - operation

- Inexpensive to construct using standard machine shop techniques
- Easy to maintain and replace corroded plates – F_2 is corrosive !
- Versatile – ready interchange of channel plates (£2 per plate)
- Ability to synthesise useful amounts of product (100 g overnight)
- Better performance than bulk, less waste

Conclusions

Gas/liquid continuous flow reactors for effective direct fluorination processes

- 1,3-Dicarbonyl derivatives (diketones, ketoesters, diesters)
- Aromatic systems

Continuous flow oxidation reactions using HOF generated *in situ*

Convenient, multi-channel flow reactors for applications to manufacturing