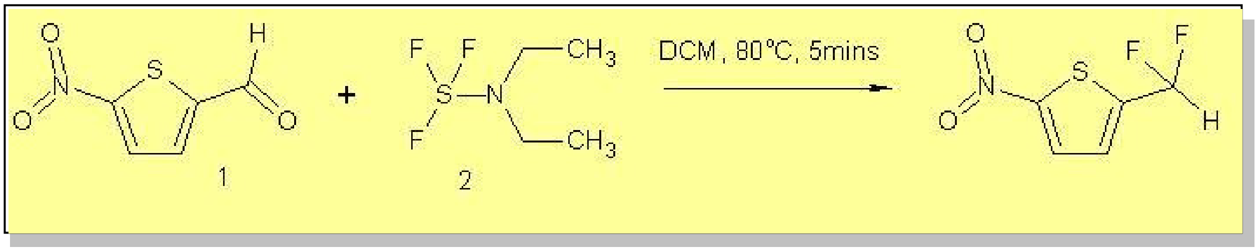
Application Note 26:
Continuous Fluorination Reaction with Diethyl Amino Sulfur Trifluoride (DAST)

This application note illustrates the use of the Vapourtec R-Series system to pump highly reactive, moisture sensitive reagents in a safe and stable continuous reaction. Here we describe the continuous fluorination of a carbonyl group with diethylaminosulfurtrifloride (DAST) pumping directly through the R-Series acid resistant pump heads.



Background

The addition of fluorine into pharmaceuticals and agrochemicals is an area of high importance and is illustrated by the number of top selling drugs containing fluorine (15 out of the top 100 selling pharmaceuticals by worldwide sales 2009). Its application also includes polymers and materials, specialty solvents, performance fluids and in numerous reagents and intermediates for chemical synthesis.

The addition of fluorine is a well-known approach to alter chemical and biological profiles, including stability, lipophilicity, bioavailability and the blocking of metabolic degradation. As such there is an increased need for safe, selective and efficient methods to introduce fluorine into molecules.

The range of fluorinating reagents is numerous and diverse covering electrophilic, nucleophilic and electrochemical approaches. Of the nucleophilic fluorinating regents the most commonly used is Diethylaminosulfur trifluoride (DAST), a reagent derived from SF_4. It is particularly useful for conversion of alcohols to alkyl fluorides, carboxylic acids to acyl fluorides and carbonyl compounds to gem-difluorides.

However the use of DAST for larger scale deoxyfluorination is limited due it reacting violently with water and having a limited thermal stability. DAST itself is a fuming, volatile liquid and difficult to handle in humid conditions and owing to its calorimetry profile can be explosive at temperatures above 90°C. DAST therefore must be handled with care

The application of flow chemistry offers several advantages here when undertaking hazardous reactions of this type including more efficient heat transfer to control thermal runaway, the ability to limit reaction volume, the decrease in handling explosive, highly toxic and corrosive reagents and the continuous replenishment of the reactants.

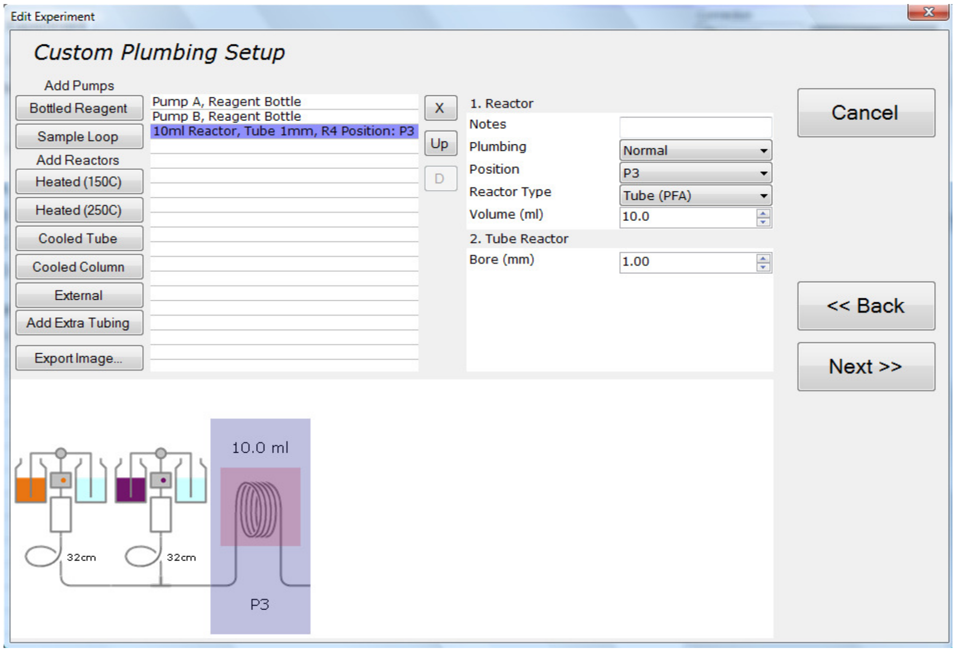
A further limitation of using these reagents in traditional batch methods are the by-products are often also highly reactive and will etch laboratory glassware. The use of the **Vapourtec R-Series** removes this issue as all reagents and by-products are only in contact with corrosion resistant components and PTFE tubing.

There are a number of publications that demonstrate the use of DAST in microfluidic systems where the reagent is introduced to the flowing stream after the pump via injection loops [i].
This study describes the use of the Vapourtec R-Series reactor to continuously feed the moisture sensitive fluorinating reagent DAST directly through the acid resistant **R2 C Plus** pump heads allowing a continuous, scalable reaction.

Method (Optimization).

As stated above, the use of injection loops after the pump head to introduce DAST to the reaction has been demonstrated. The aim here is to demonstrate the continuous pumping with no detrimental decomposition and no decrease in reactivity of the reagent. Initial experiments involved pumping small aliquots of both substrate and fluorinating reagent through the pump head to measure this.

It is important that the drying procedure for running moisture sensitive reagents such as DAST is carried out as any residual moisture will result in decomposition of the reagent generating HF. Vapourtec have developed protocols for a variety of water and/or air sensitive reagents which are freely available to all Vapourtec R-Series users.
For this study the Vapourtec “DAST protocol” was used.



Pump A, Reagent Bottle
Pump B, Reagent Bottle
10ml Reactor, Tube 1mm, R4 Position: P3

1. Reactor
Notes
Plumbing: Normal
Position: P3
Reactor Type: Tube (PFA)
Volume (ml): 10.0
2. Tube Reactor
Bore (mm): 1.00

Fig 1. FlowCommander™ setup for the experiment.

Setup

The flow reactor was configured using a combination of the **R2 C Plus** pump module and **R4** reactor module as shown in Figs 1.

A 10 ml PFA reactor was installed along with an 8 bar Vapourtec acid resistant back pressure regulator (BPR) fitted in-line between the reactor outflow and the collection valve.

A 20ml stock solution of the reagents was prepared in anhydrous DCM;

Solution A

0.25M of the substrate **1,** 5-Nitro-2-thiophenecarboxaldehyde (Aldrich 302295, CAS 4521-33-1)

Solution B

0.50M Substrate **2**, diethylaminosulfurtrifluoride (DAST), (Aldrich 31942, CAS 38078-09-0)

System Parameters

System solvent:	DCM
Reagent A:	0.25M substrate 1
Reagent B:	0.50M substrate 2
Flow rate A:	variable (167 – 1000 µL/min)
Flow rate B:	variable (167 – 1000 µL/min
Stiochiometry A:B	1:2
Reactor volume:	10 mL PFA reactor
Reactor temperature:	80 ℃
Back pressure regulator:	~8 bar. Vapourtec Acid resistant BPR (with 1mm bore throughout).

Then the following sequence of events was carried out for each reaction

1) The system was fully dried as per the protocol.
2) *Priming the pumps with anhydrous DCM:* Both selection valves were set to 'Solvent' and the pumps were `primed with anhydrous DCM under a nitrogen atmosphere at 1.0 mL/min per pump.
3) *Priming the pumps with reagents:* The selection valve for line 1 was set to 'Reagent', the pumps set to 1 mL/min and the line connecting the valves to stock bottle 1 was filled with **Solution A.** The selection valve was set back to 'Solvent' and anhydrous DCM pumped through the lines for 2 minutes. The same process was repeated with line 2**, Solution B** to fill the second reagent line.

4) *Reaction optimization:* A selective range of conditions were run using FlowCommander™ software. Residence times of 5, 10, 15 and 30 minutes were run at with a fixed stoichiometry (2.0eq DAST) in a 10ml reactor at 80^{o}C. A 4ml aliquot of solution A (1.0mM substrate 1) was reacted in each experiment.

5) *Work-Up and Analysis:* The collection stream was directed into a vial containing a 10% solution of NaHCO$_3$ to quench the reaction. The product was extracted with DCM, washed with a saturated solutions of NaHCO$_3$ and then brine, dried (MgSO$_4$) and concentrated *in-vacuo* to dryness.

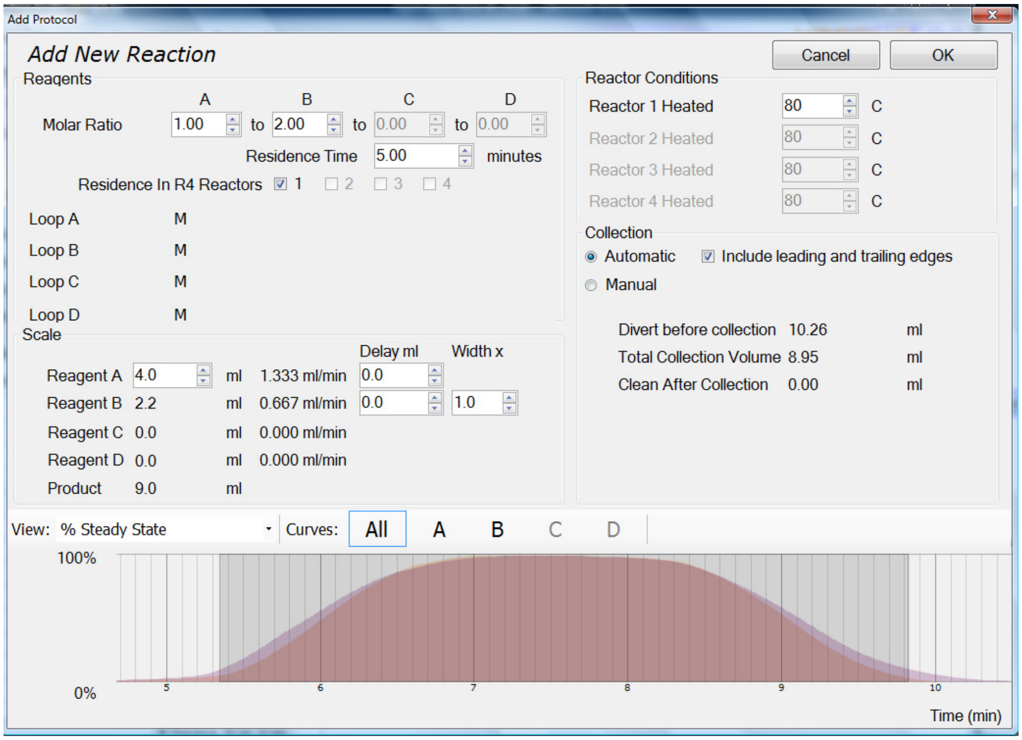
The reactions were followed by TLC (SiO$_2$, 1:1 EtOAc:Hexane, UV detection) and RP HPLC.

The initial reaction conditions of a 30min residence time at 80°C with the 2.0eq of DAST required showed a quantitative conversion to the desired product.

A reduction of residence time was explored (to increase the mass transfer). At residence times of 15, 10 and 5 minutes a quantitative conversion was also observed.

Again to increase mass transfer, the concentration of solution B was increased to 1.0M. Note due to the solubility of substrate 1, the concentration of solution A could not be increased. Repeating the experiment at 5mins residence time, 80°C and 2.0eq DAST again gave a quantitative conversation by TLC/HPLC.

Fig 2 shows the FlowCommander™ reaction setup for this reaction.



Reagents

	A		B		C		D
Molar Ratio	1.00	to	2.00	to	0.00	to	0.00

Residence Time 5.00 minutes

Residence In R4 Reactors ☑ 1 ☐ 2 ☐ 3 ☐ 4

Loop A M
Loop B M
Loop C M
Loop D M

Scale

				Delay ml	Width x
Reagent A	4.0	ml	1.333 ml/min	0.0	
Reagent B	2.2	ml	0.667 ml/min	0.0	1.0
Reagent C	0.0	ml	0.000 ml/min		
Reagent D	0.0	ml	0.000 ml/min		
Product	9.0	ml			

Reactor Conditions

Reactor 1 Heated 80 C
Reactor 2 Heated 80 C
Reactor 3 Heated 80 C
Reactor 4 Heated 80 C

Collection

● Automatic ☑ Include leading and trailing edges
○ Manual

Divert before collection 10.26 ml
Total Collection Volume 8.95 ml
Clean After Collection 0.00 ml

View: % Steady State

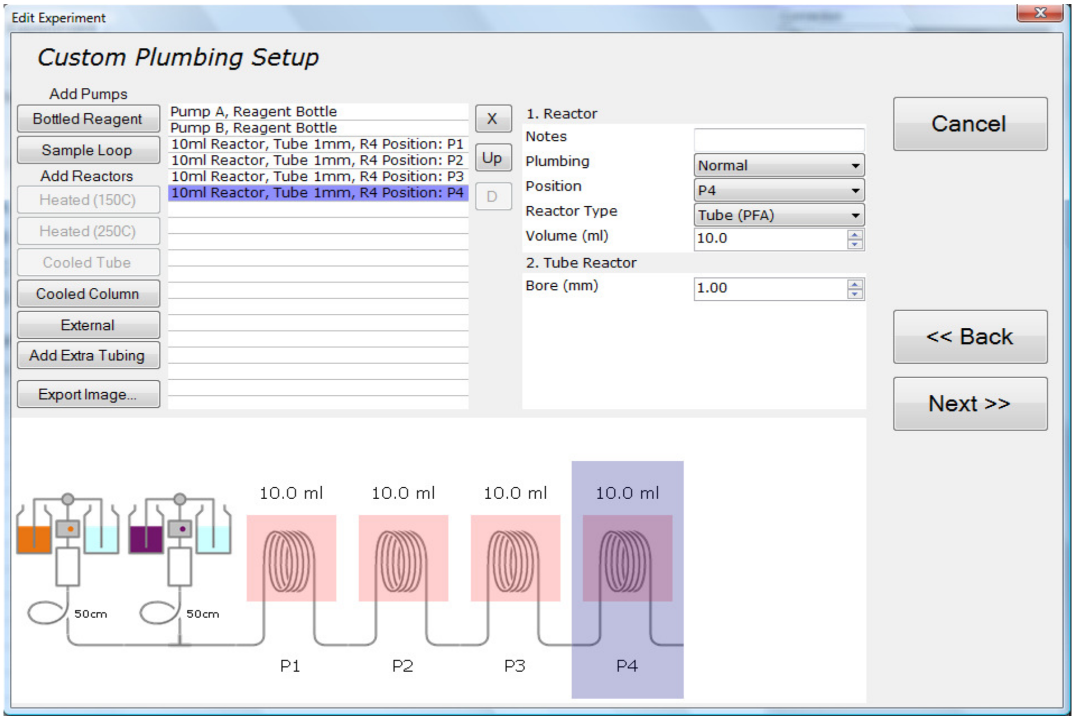
Fig 2 . Reaction setup showing
- **reaction conditions**
- **predicted dispersion profile at the collection point**

Method (Steady State Conditions)

As described the optimum reaction conditions for reacting a dispersed 4ml aliquot were 80^{o}C, 5mins residence time with 2.0eq DAST.

The predicted dispersion profile from this reaction (see base of fig 2) shows a significant steady state region and showed a quantitative conversion (by TLC/HPLC) with these conditions.

These two factors make it reasonable to assume that the reaction can be not only run in a continuous steady state but also scaled further by using the Vapourtec R-series capabilities of placing four reactors in series, as shown in Fig 3.



Pump A, Reagent Bottle
Pump B, Reagent Bottle
10ml Reactor, Tube 1mm, R4 Position: P1
10ml Reactor, Tube 1mm, R4 Position: P2
10ml Reactor, Tube 1mm, R4 Position: P3
10ml Reactor, Tube 1mm, R4 Position: P4

1. Reactor

Notes	
Plumbing	Normal
Position	P4
Reactor Type	Tube (PFA)
Volume (ml)	10.0

2. Tube Reactor

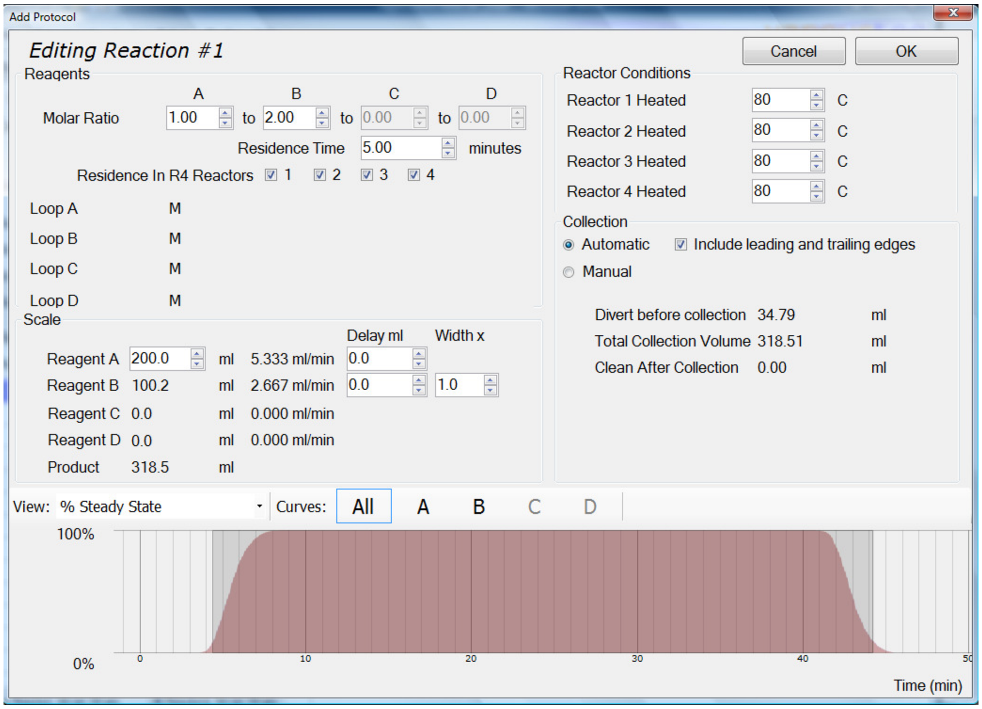
Bore (mm)	1.00

Fig 3 . Experimental Setup for scale-up

Setup

Fig 4 shows the reaction setup in FlowCommander™ .

Note that the 5mins residence time is applied to the combined reactor formed by the four individual reactors in series.



Editing Reaction #1

Reagents

	A		B		C		D
Molar Ratio	1.00	to	2.00	to	0.00	to	0.00

Residence Time 5.00 minutes

Residence In R4 Reactors ☑ 1 ☑ 2 ☑ 3 ☑ 4

Loop A M
Loop B M
Loop C M
Loop D M

Scale

				Delay ml	Width x
Reagent A	200.0	ml	5.333 ml/min	0.0	
Reagent B	100.2	ml	2.667 ml/min	0.0	1.0
Reagent C	0.0	ml	0.000 ml/min		
Reagent D	0.0	ml	0.000 ml/min		
Product	318.5	ml			

Reactor Conditions

Reactor 1 Heated	80	C
Reactor 2 Heated	80	C
Reactor 3 Heated	80	C
Reactor 4 Heated	80	C

Collection

● Automatic ☑ Include leading and trailing edges
○ Manual

Divert before collection	34.79	ml
Total Collection Volume	318.51	ml
Clean After Collection	0.00	ml

View: % Steady State

Fig 4 – Reaction set-up for scale-up

Stock solutions of the reagents were prepared in anhydrous DCM;

Solution A
0.25M of the substrate **1,** 5-Nitro-2-thiophenecarboxaldehyde (Aldrich 302295, CAS 4521-33-1) (200ml, 50mM)

Solution B
1.00M Substrate **2**, diethylaminosulfur trifluoride (DAST), (Aldrich 31942, CAS 38078-09-0) (100ml, 100mM)

System Parameters

System solvent:	DCM
Reagent A:	0.25M substrate 1
Reagent B:	1.00M substrate 2
Flow rate A:	5.333 mL/min
Flow rate B:	2.667 mL/min
Stiochiometry A:B	1:2
Reactor volume:	40 mL (4x 10ml PFA reactor)
Reactor temperature:	80 ℃
Back pressure regulator:	~8 bar. Acid resistant BPR used with 1mm bore throughout.

The sequence of events was repeated from the optimization experiments.

1) The system was fully dried as outlined above. This was repeated to ensure the extra reactors used were fully dried.

2) *Priming the pumps with anhydrous DCM:* Both selection valves were set to ‘Solvent’ and the pumps were `primed with anhydrous DCM under a nitrogen atmosphere at 1.0 mL/min per pump.
3) *Priming the pumps with reagents:* The selection valve for line 1 was set to ‘Reagent’, the pumps set to 1 mL/min and the line connecting the valves to stock bottle 1 was filled with **Solution A.** The selection valve was set back to ‘Solvent’ and anhydrous DCM pumped through the lines for 2 minutes. The same process was repeated with line 2**, Solution B** to fill the second reagent line.

4) *Steady State Reaction:* A residence times of 5 minutes was set at 80^{o}C with a stoichiometry (2.0eq DAST) in a 40ml reactor (4 x 10ml PFA reactors in series). 200ml of solution A was reacted.

5) *Work-Up and Analysis:* The collection stream was directed into a vial containing a 10% solution of $NaHCO_3$ to quench the reaction. The product was extracted with DCM, washed with a saturated solutions of $NaHCO_3$ and then brine, dried ($MgSO_4$) and concentrated *in-vacuo* to dryness.

Results

Optimisation Experiment

4 ml of **solution A** (1mmol) was processed and collected over ~4.5 mins as shown above, fig. 2. After work-up the extracted material gave a straw coloured oil. Yield = 0.166g, 93%. Note the product was not purified further as NMR indicated 100% purity.

Steady State Experiment (Scale-Up)

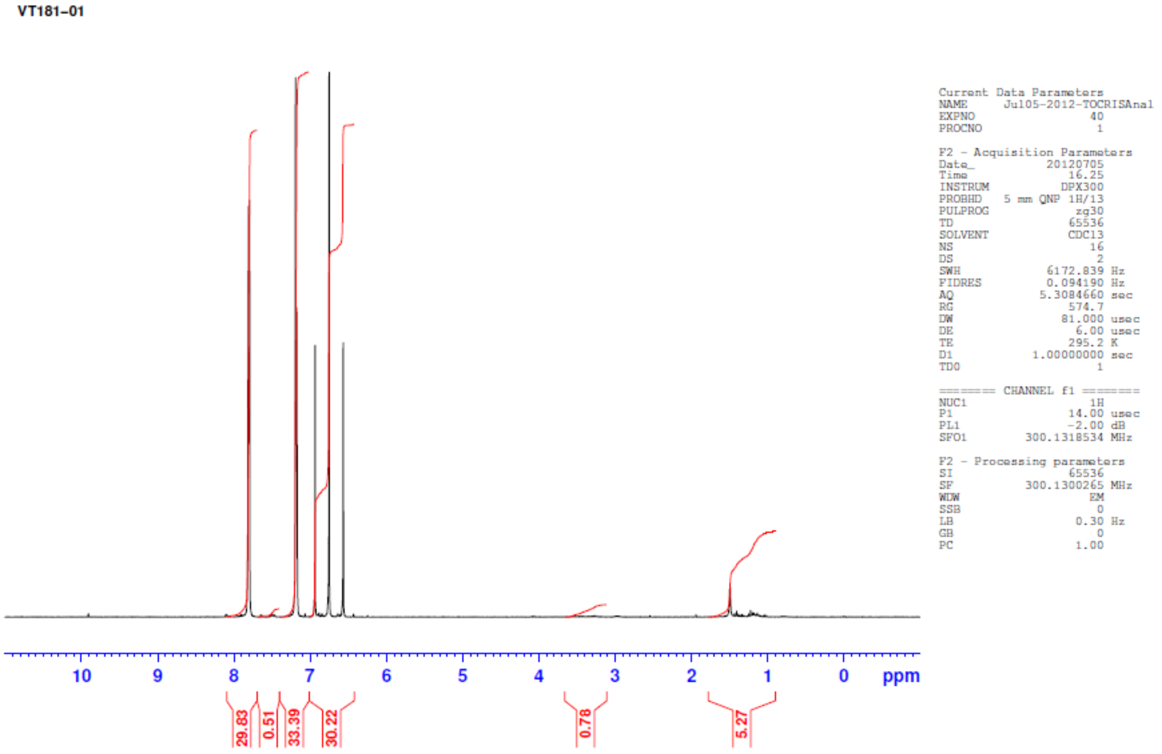
200 ml of **solution A** (50mmol) was processed and collected over ~37.5 mins as shown above. After work-up the extracted material gave a straw coloured oil. Yield = 8.495g, 95%. Note the product was not purified further as HPLC indicated 97.5% purity.

The yield of 8.5g over just under 40mins is equal to a mass transfer of ~13.6g /hr. Extrapolating this experiment we can predict a yield of ~325g/ 25hrs under continuous reaction conditions.

NMR Analysis

VT181-01 4ml Optimization Experiment.

^{1}H NMR



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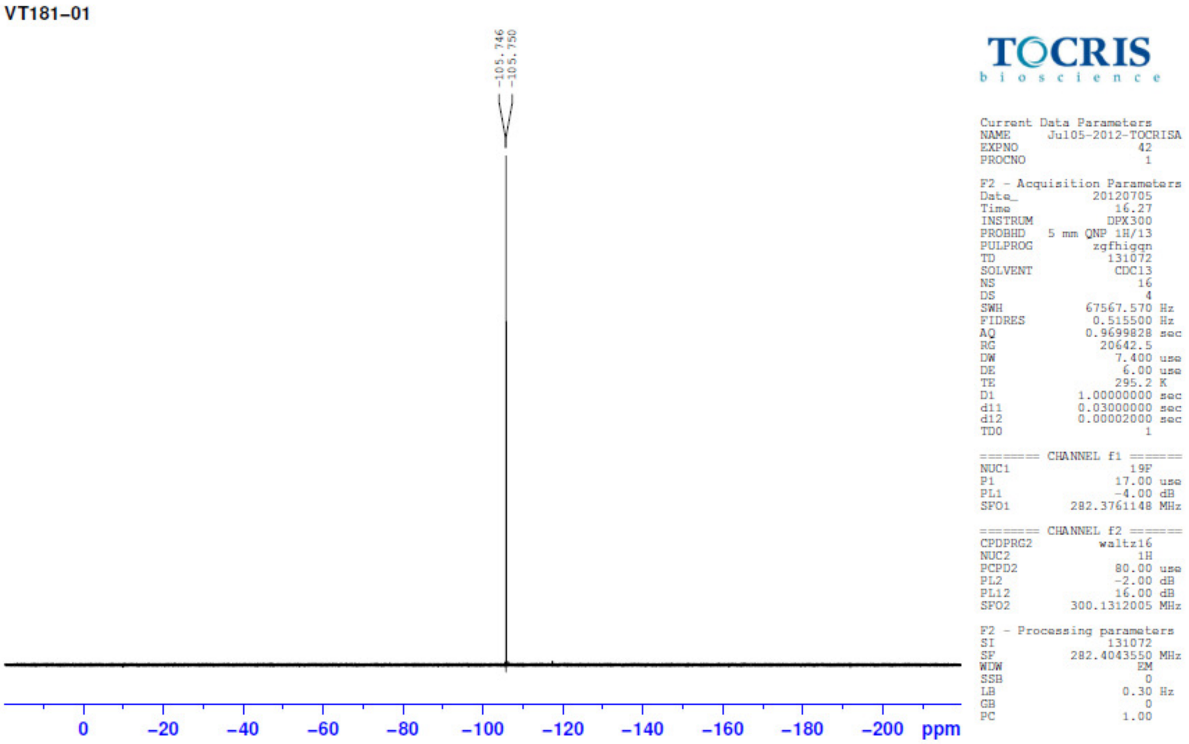
PULPROG               zg30
TD                   65536
SOLVENT              CDC13
NS                      16
DS                       2
SWH              6172.839 Hz
FIDRES           0.094190 Hz
AQ              5.3084660 sec
RG                   574.7
DW                  81.000 usec
DE                    6.00 usec
TE                   295.2 K
D1             1.00000000 sec
TD0                      1

======= CHANNEL f1 =======
NUC1                    1H
P1                   14.00 usec
PL1                  -2.00 dB
SFO1           300.1318534 MHz

F2 - Processing parameters
SI                   65536
SF             300.1300265 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```

19F NMR (F decoupled)



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PROCNO                     1

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Time                   16.27
INSTRUM               DPX300
PROBHD     5 mm QNP 1H/13
PULPROG             zgfhiggn
TD                    131072
SOLVENT                CDCl3
NS                        16
DS                         4
SWH                67567.570 Hz
FIDRES              0.515500 Hz
AQ                 0.9699828 sec
RG                   20642.5
DW                     7.400 use
DE                      6.00 use
TE                     295.2 K
D1                1.00000000 sec
d11               0.03000000 sec
d12               0.00002000 sec
TD0                        1

======= CHANNEL f1 ======
NUC1                     19F
P1                     17.00 use
PL1                    -4.00 dB
SFO1             282.3761148 MHz

======= CHANNEL f2 ======
CPDPRG2              waltz16
NUC2                      1H
PCPD2                  80.00 use
PL2                    -2.00 dB
PL12                   16.00 dB
SFO2             300.1312005 MHz

F2 - Processing parameters
SI                    131072
SF               282.4043550 MHz
WDW                       EM
SSB                        0
LB                      0.30 Hz
GB                         0
PC                      1.00
```
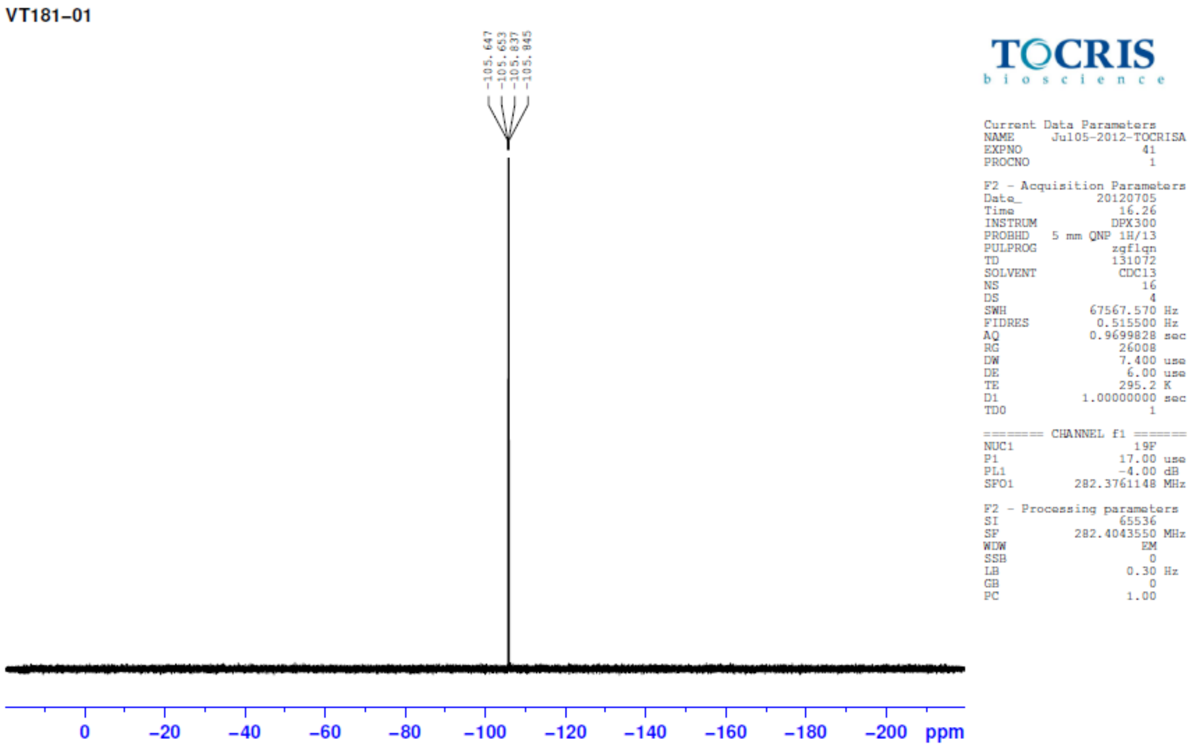

19F NMR (F coupled)



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PROCNO                     1

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PULPROG               zgflqn
TD                    131072
SOLVENT                CDCl3
NS                        16
DS                         4
SWH                67567.570 Hz
FIDRES              0.515500 Hz
AQ                 0.9699828 sec
RG                     26008
DW                     7.400 use
DE                      6.00 use
TE                     295.2 K
D1                1.00000000 sec
TD0                        1

======= CHANNEL f1 ======
NUC1                     19F
P1                     17.00 use
PL1                    -4.00 dB
SFO1             282.3761148 MHz

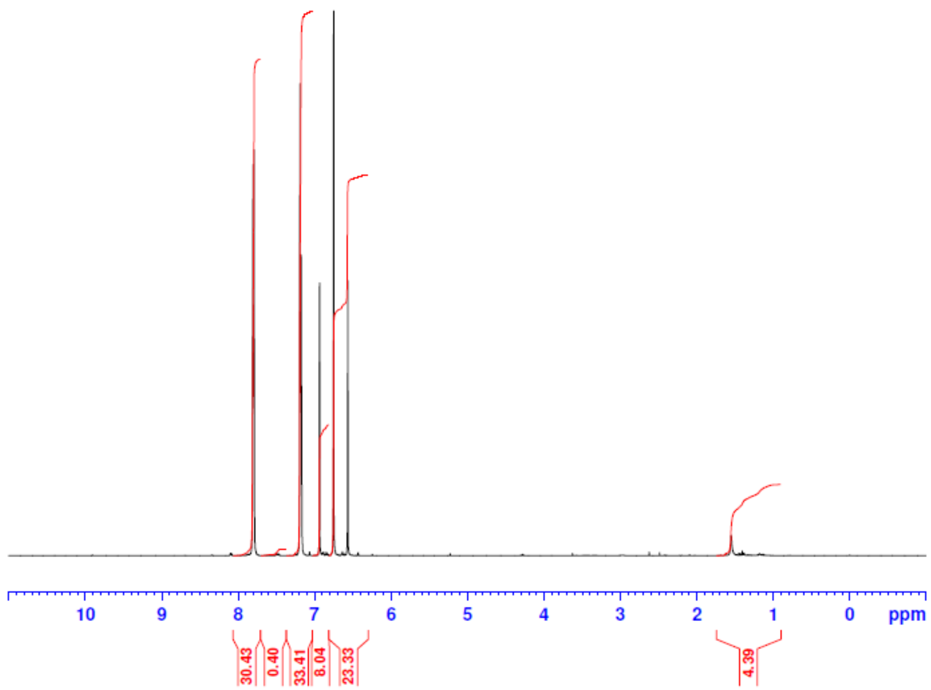
F2 - Processing parameters
SI                     65536
SF               282.4043550 MHz
WDW                       EM
SSB                        0
LB                      0.30 Hz
GB                         0
PC                      1.00
```

Waiting on NMR analysis for the larger scale reaction, should have these tomorrow.

VT192-01 Steady State Experiment (Scale-Up)

^{1}H NMR

VT192–01



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PROCNO                  1

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PULPROG              zg30
TD                  65536
SOLVENT             CDC13
NS                     16
DS                      2
SWH              6172.839 Hz
FIDRES           0.094190 Hz
AQ              5.3084660 sec
RG                  406.4
DW                 81.000 usec
DE                   6.00 usec
TE                  298.2 K
D1             1.00000000 sec
TD0                     1

======= CHANNEL f1 =======
NUC1                   1H
P1                  14.00 usec
PL1                 -2.00 dB
SFO1          300.1318534 MHz

F2 - Processing parameters
SI                  65536
SF            300.1300269 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```
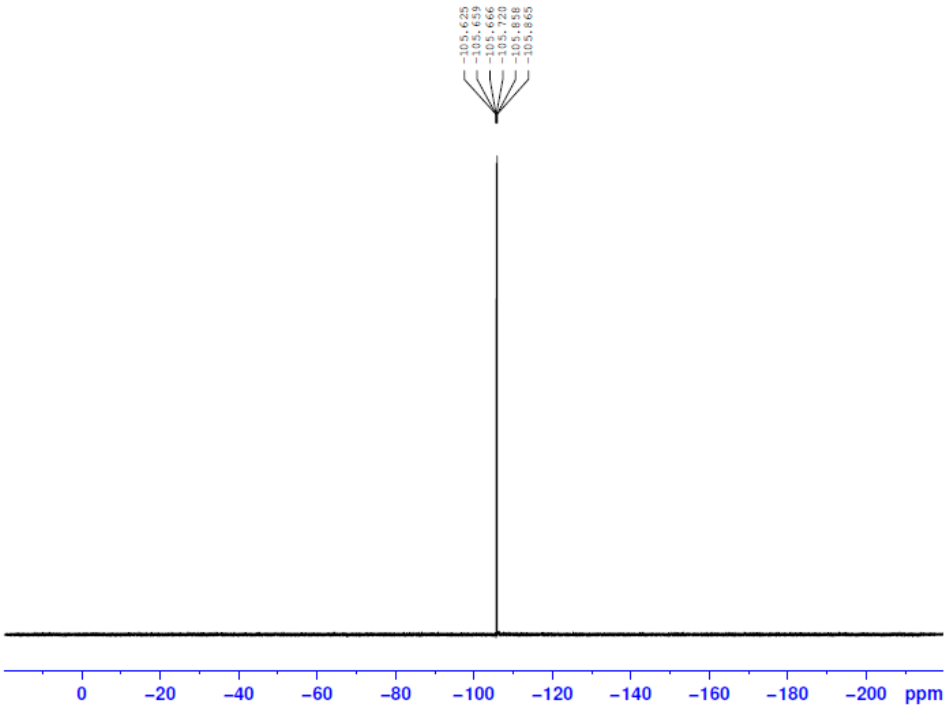

19F NMR (F decoupled)



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PROCNO                  1

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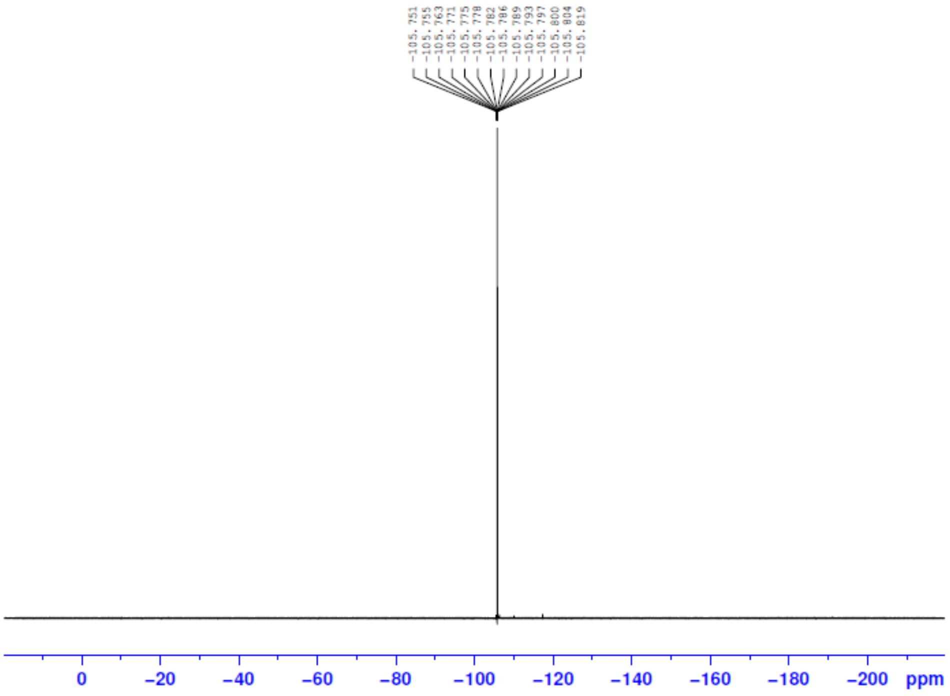
PROBHD   5 mm QNP 1H/13
PULPROG            zgflqn
TD                 131072
SOLVENT             CDC13
NS                     16
DS                      4
SWH             67567.570 Hz
FIDRES           0.515500 Hz
AQ              0.9699828 sec
RG                  16384
DW                  7.400 usec
DE                   6.00 usec
TE                  298.2 K
D1             1.00000000 sec
TD0                     1

======= CHANNEL f1 =======
NUC1                  19F
P1                  17.00 usec
PL1                 -4.00 dB
SFO1          282.3761148 MHz

F2 - Processing parameters
SI                  65536
SF            282.4043550 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```

19F NMR (F coupled)

VT192–01



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PROCNO                   1

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PULPROG           zgfhigqn
TD                  131072
SOLVENT              CDC13
NS                      16
DS                       4
SWH              67567.570 Hz
FIDRES            0.515500 Hz
AQ               0.9699828 sec
RG                 14596.5
DW                   7.400 use
DE                    6.00 use
TE                   298.2 K
D1              1.00000000 sec
d11             0.03000000 sec
d12             0.00002000 sec
TD0                      1

======= CHANNEL f1 =======
NUC1                   19F
P1                   17.00 use
PL1                  -4.00 dB
SFO1           282.3761148 MHz

======= CHANNEL f2 =======
CPDPRG2            waltz16
NUC2                    1H
PCPD2                80.00 use
PL2                  -2.00 dB
PL12                 16.00 dB
SFO2           300.1312005 MHz

F2 - Processing parameters
SI                  131072
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SSB                      0
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```
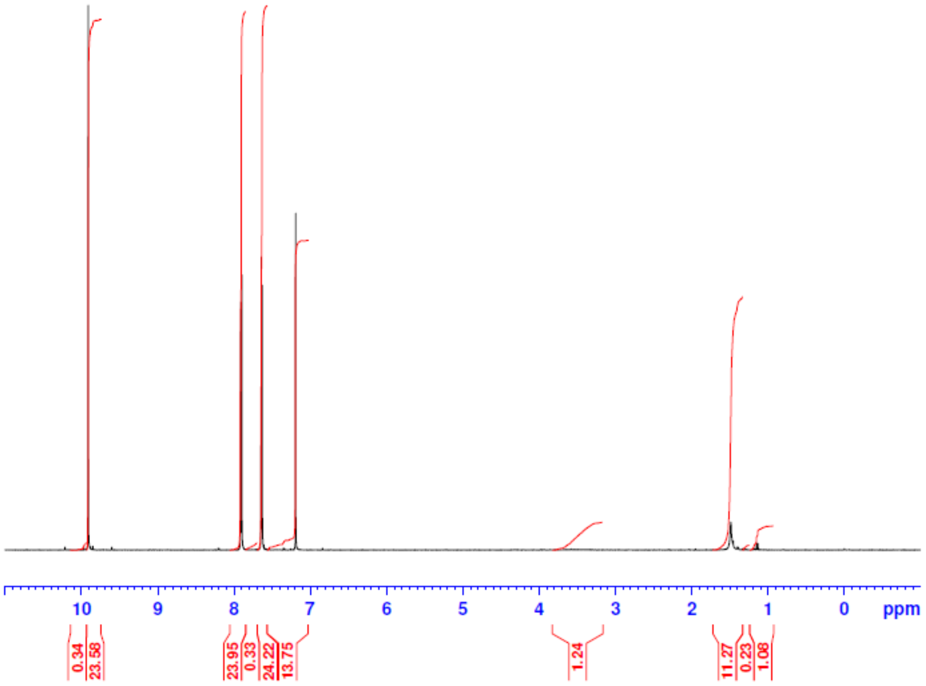

VT192-SM, ^{1}H NMR

VT192–SM



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TD                   65536
SOLVENT              CDC13
NS                      16
DS                       2
SWH               6172.839 Hz
FIDRES            0.094190 Hz
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RG                  1824.6
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DE                    6.00 usec
TE                   298.2 K
D1              1.00000000 sec
TD0                      1

======= CHANNEL f1 =======
NUC1                    1H
P1                   14.00 usec
PL1                  -2.00 dB
SFO1           300.1318534 MHz

F2 - Processing parameters
SI                   65536
SF             300.1300266 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
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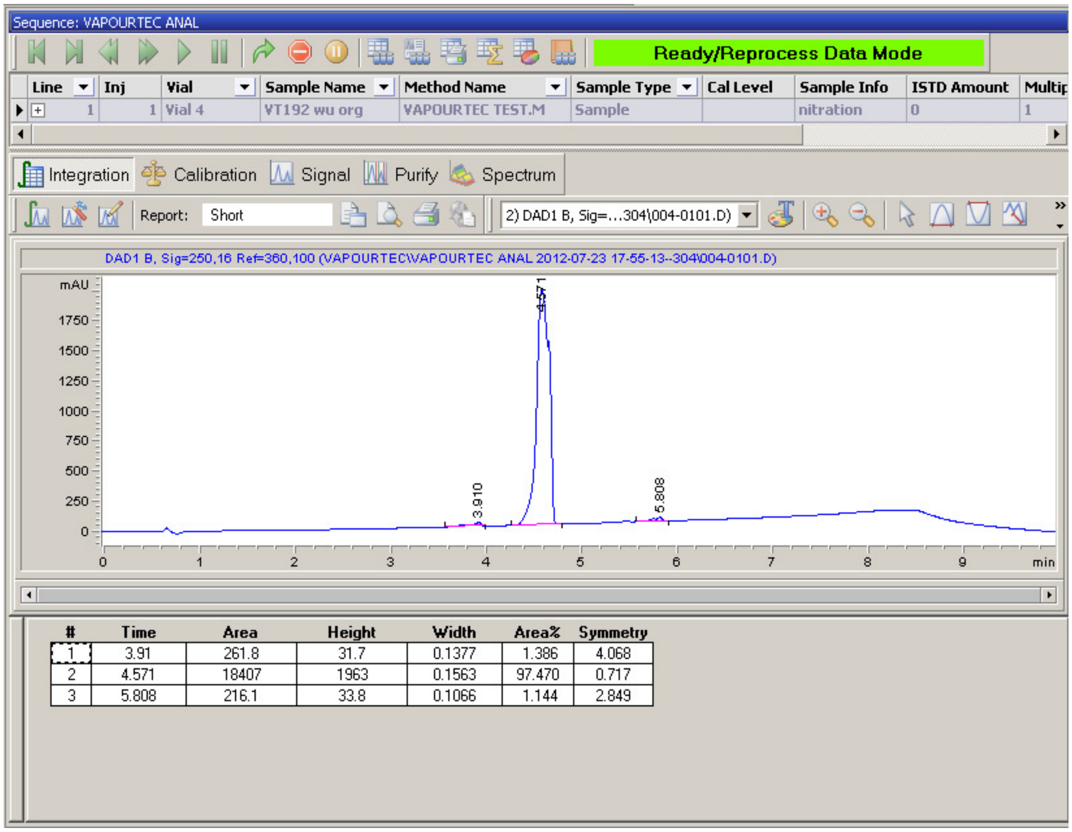
HPLC Analysis

VT192-01 Steady state experiment



Line	Inj	Vial	Sample Name	Method Name	Sample Type	Cal Level	Sample Info	ISTD Amount	Multip
1	1	Vial 4	VT192 wu org	VAPOURTEC TEST.M	Sample		nitration	0	1

Report: Short

2) DAD1 B, Sig=...304\004-0101.D)

DAD1 B, Sig=250,16 Ref=360,100 (VAPOURTEC\VAPOURTEC ANAL 2012-07-23 17-55-13--304\004-0101.D)

#	Time	Area	Height	Width	Area%	Symmetry
1	3.91	261.8	31.7	0.1377	1.386	4.068
2	4.571	18407	1963	0.1563	97.470	0.717
3	5.808	216.1	33.8	0.1066	1.144	2.849

Conclusion

It has been shown that the bench top Vapourtec R-Series system can safely and stably perform nucleophilic fluorinations to scale with diethylaminosulfur trifluoride (DAST) pumping directly through the R2 C Plus acid resistant pump heads. The conversion of the electron rich aldehyde system shows a general, easy to use protocol. Further to this it has been shown that potentially difficult to handle reagents when used in a batch reaction can be easy to use in a continuous flow system

Acknowledgements

Vapourtec would like to thank Andrew Mansfield of Flow Chemistry Solutions Ltd
for his assistance with this application note

andrew.mansfield@flowchemistrysolutions.co.uk
www.flowchemistrysolutions.co.uk

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[i] (a) Marcus Baumannn, Ian R. Baxendale, Steven V. Ley, Synlett, **2008**, 14, 2111-2114;

(b) Marcus Baumann, Ian R. Baxendale, Laetitia J. Martin, Steven V. Ley, Tetrahedron, **2009**, 65, 6611-6625;

(c) Tomas Gustafsson, Ryan Gilmour, Peter H. Seeberger, **2008**, 3022-3024.