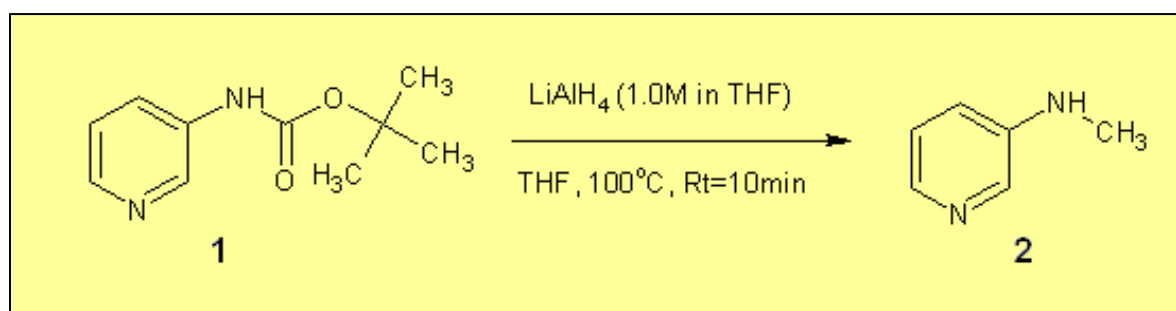


## Application Note 22

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### Continuous Reduction of N-Boc Protected Amines to N-Me Amines using Lithium Aluminium Hydride.

This example illustrates the use of the Vapourtec R-Series system to carry out reactions with moisture sensitive, highly reactive reagents under flow conditions. It demonstrates how the proper drying procedure allows the Vapourtec R2 pump to handle this highly water sensitive reagent.



### Background

Lithium aluminium hydride (LiAlH<sub>4</sub>) is widely used in organic chemistry as a reducing agent. It is more powerful than the related reagent sodium borohydride due to the weaker Al-H bond compared to the B-H bond. It will reduce a variety of functionalities but is mainly used to convert esters, carboxylic acids, aldehydes and ketones to the corresponding alcohols. In this example we show the reduction of an *N-tert*-butoxycarbonyl (N-Boc) protected substrate directly to the analogous N-methyl group. There are a very limited number of literature examples of aryl N-Boc systems (mainly aniline derivatives) using this transformation and even fewer with heteroaromatic N-Boc systems. The ability to N-methylate these species in a controlled, chemo selective manner is a great advantage over more traditional N-methylation methods.

## Reaction Optimisation

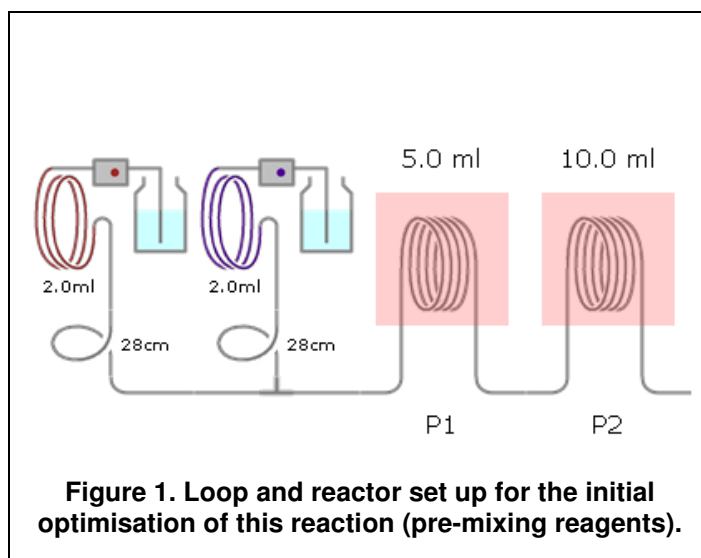
Initially a short reaction optimisation sequence was carried out to determine the optimum temperature, residence time, and stoichiometry of the reducing reagent.

### Setup (Optimisation)

These initial experiments used sample injection loops to feed the reagents.

The substrate and the reducing agent were first fed from the loops through a T mixer.

A premixing period was then included (a 5ml reactor kept at room temperature, P1 in Fig 1) before the main reactor (P2). This method is analogous to how this reaction would be carried out in batch.



A 100 psi back pressure regulator was fitted after the reactors.

The reactor outflow by-passed the collection valve and instead was directed straight into the collection vessel after a short length of tubing.

### Method (Optimisation)

Reagent stock solutions were prepared;

- solution A (0.2M of the substrate **1** in THF)
- solution B (1.0M LiAlH<sub>4</sub> in THF – Aldrich [212776](#), CAS [16853-85-3](#)).

The collection vessel was a 50 mL glass flask containing 0.2M NaOH<sub>(aq)</sub> to quench the reaction product.

It is important that the drying procedure for running organometallic reagents such as LiAlH<sub>4</sub> is carried out as any residual moisture will result in lithium salts precipitating in the pumps which will prevent the correct functioning of the pump check valve. If the pumps are run for extended periods in this state, the pistons can become lined with these salts, which in turn cause the seals to be ground away, followed by leakage into the backwash area of the pump.

Vapourtec supply a protocol for drying the pumps and pipework prior to pumping with LiAlH<sub>4</sub>. This was followed.

Note that the anhydrous solvents were kept under a pressurised dry inert atmosphere. This was achieved with a separate low pressure N<sub>2</sub> supply. Newer Vapourtec systems have an inert gas manifold built in, removing the need for regulation of inert gas pressure.

After the protocol has been followed, the system is dry enough to introduce the reagents under inert conditions.

### Summary

*System solvent:* DCM

*Reagent A:* 0.2M substrate **1** (2 mmol) in THF (10 mL)

*Reagent B:* 1.0M LiAlH<sub>4</sub> in THF

*Flow rate A:* variable (417 – 1667 μL/min)

*Flow rate B:* variable (83 – 333 μL/min)

*Stoichiometry A:B:* variable 1.2eq, 2.0eq and 4.0eq amine.

*Reactor volume:* 10 mL PFA

*Reactor temperature:* variable 80 - 120 °C

*Back pressure regulator:* 100 psi

Note that for 1:1 stoichiometric ratio, the two reagents must be pumped at a flow rate ratio of 5:1 because of the different concentrations.

### Running the Reaction (Optimisation)

1. *Pump Drying* The system was thoroughly dried following the specified protocol
2. *Priming the sample loops with reagents:* The selection valve for each sample loop was set to 'Load', the pumps set to 1 mL/min and the desired solution manually injected via the rheodyne valve input. Solution A in loop A and solution B into loop B. Note: The LiAlH<sub>4</sub> solution is kept under an inert atmosphere. Care should be taken when injecting this reagent manually
3. *Reaction optimisation:* A range of conditions were run manually. Residence times of 5, 10 and 20 minutes were run at two variations of LiAlH<sub>4</sub> stoichiometry (1.0eq, 1.5eq) in a 10ml reactor at 100 and 120°C. (The premixing reactor was kept at 25°C)
4. *Reaction Work-Up:* The outflow was directed in a flask containing 0.2M NaOH<sub>(aq)</sub>. The resulting lithium salts were filtered, washed with further 0.2M NaOH<sub>(aq)</sub> and the filtrate extracted with EtOAc. This was repeated with any ppt formed in the extraction. The organics were combined, dried and evaporated to dryness *in-vacuo*.

The reactions were followed by TLC (SiO<sub>2</sub>, 20% MeOH/DCM, UV detection) after the workup procedure. It should be noted that acidic methods of hydrolysing the lithium salts were not used as this would have removed the N-Boc group from any remaining SM.

## Results (Optimisation)

All reactions carried out at 80°C showed some of the starting material **1** present, even with an excess of the reducing reagent (1.5eq) and Rt=20mins. Increasing the reaction temperature to 100°C showed complete conversion by TLC at both extremes of conditions

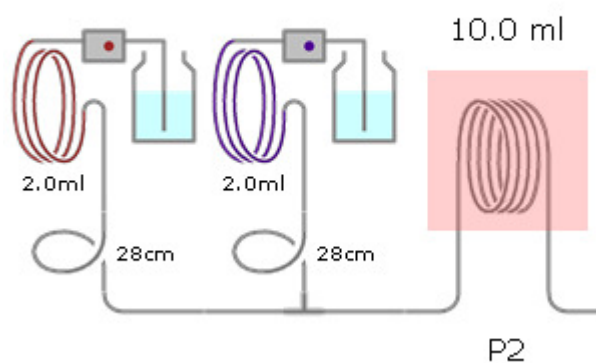
(100°C, Rt=5min, 1.0eq LiAlH<sub>4</sub> – 100°C, Rt=20mins, 1.5eq LiAlH<sub>4</sub>).

## Is the pre-mixing necessary ?

To investigate if the pre-mixing of reagents was necessary the 1<sup>st</sup> (premixing) reactor was removed

Repeating the conditions run previously of

- 100°C,
- Rt=5mins,
- 1.0eq LiAlH<sub>4</sub>



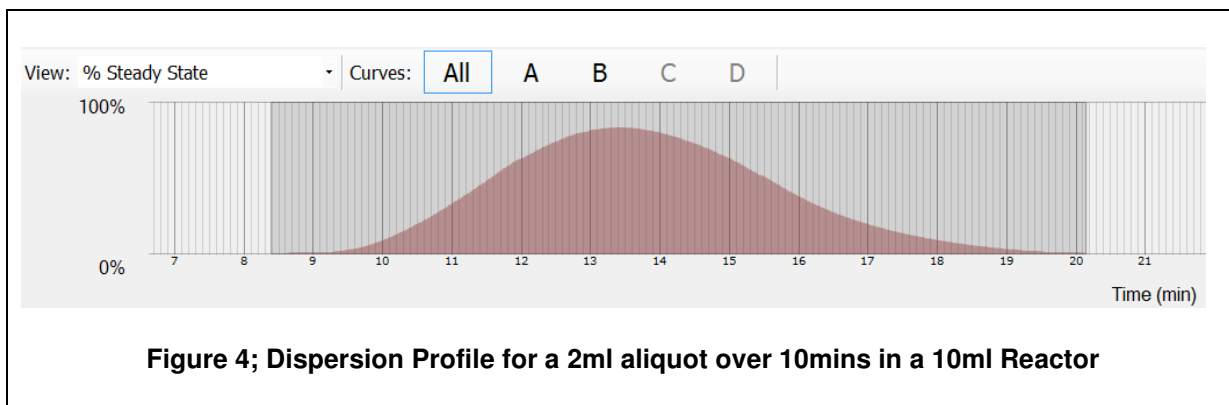
**Figure 3: Reactor setup without pre-mixing**

showed complete conversion by TLC, indicating that pre-mixing was not necessary.

## Scaleup

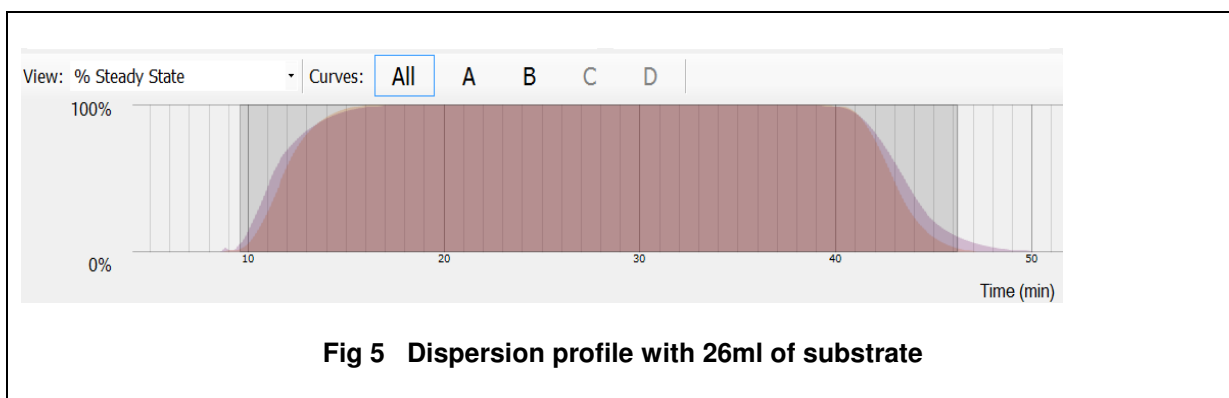
It is to be noted that these results were obtained by effectively introducing a 2.4ml aliquot of the reaction mixture (because of the 5:1 flow rates, we effectively bring together 2ml of substrate and 0.4ml of  $\text{LiAlH}_4$ ) via the injection loop into a 10ml reactor. The dispersion profile obtained from this is significant as shown below (output from the Vapourtec FlowCommander™ dispersion modeller)

This illustrates that the concentration of the sample would not have reached the initial 0.2M concentration.



This means that for representative state results a larger volume must be processed.

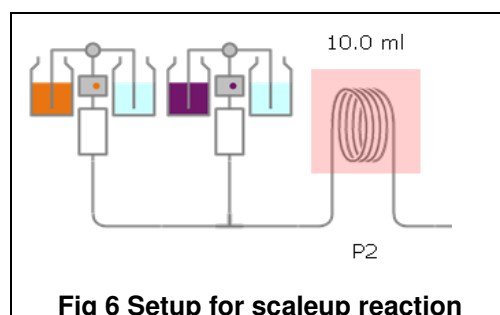
Figure 5 shows the dispersion profile for a much larger scale reaction.



## Setup (Scale up)

The configuration was altered from the optimisation reactions.

The sample loops were by-passed with the reagents introduced directly through the pumps.



## Method (Scaleup)

The optimum reaction conditions from the previous step were 100°C, for 10mins residence time (no premixing) with 1.0eq LiAlH<sub>4</sub>.

These conditions were then investigated on a reaction that had reached steady state. The reaction was then run on a 5.2mmol scale (0.2M, 26ml).

As described for the optimisation experiments it is important to ensure that the pumps and tubing are fully dried prior to running the reaction with LiAlH<sub>4</sub> solution, and that anhydrous solvents are kept under an inert atmosphere.

Note that the Vapourtec protocol for pumping LiAlH<sub>4</sub> includes details of how to leave the pumps between experiments for optimal performance when restarting.

### Summary:

*System solvent:* DCM

*Reagent A:* 0.2M substrate **1** (5.2mmol) in THF (26 mL)

*Reagent B:* 1.0M LiAlH<sub>4</sub> in THF

*Flow rate A:* 833µL/min)

*Flow rate B:* 167µL/min)

*Stoichiometry A:B:* 1:1

*Reactor volume:* 10 mL PFA

*Reactor temperature:* variable 100 °C

*Back pressure regulator:* 100 psi

## Running the Main Reaction (scale-up)

The reaction was run , using FlowCommander™ under the conditions described above.

26 ml of solution A were processed and the steady state region as described by the Flow Commanders dispersion profile was collected over 30mins.

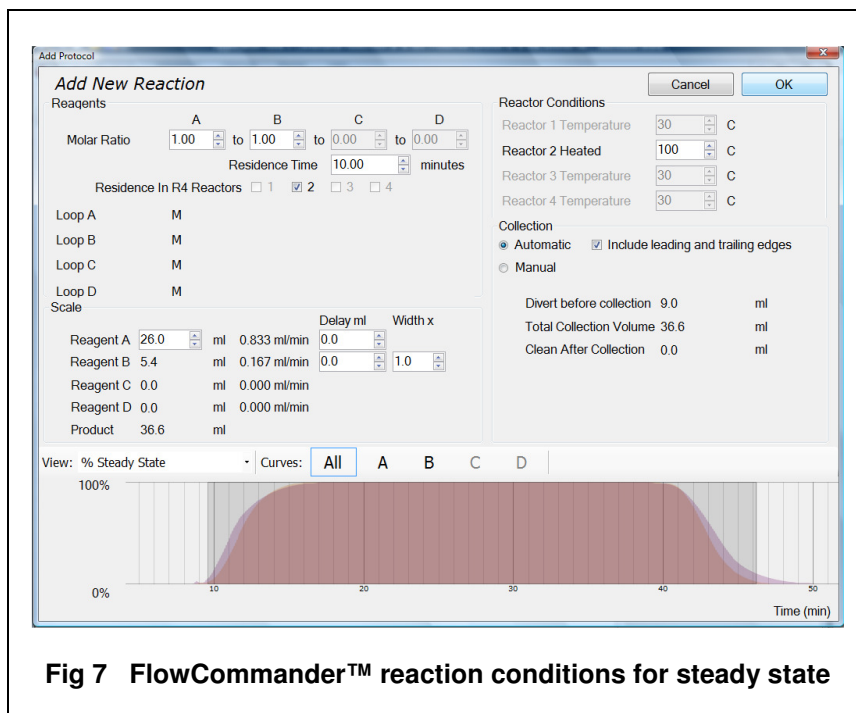


Fig 7 FlowCommander™ reaction conditions for steady state

## Reaction Work-Up:

The outflow was directed in a flask containing 0.2M NaOH<sub>(aq)</sub>. The resulting lithium salts were filtered, washed with further 0.2M NaOH<sub>(aq)</sub> and the filtrate extracted with EtOAc. This was repeated with any ppt formed in the extraction. The organics were combined, dried and evaporated to dryness *in-vacuo*. This gave a pale yellow gum which was further purified by column chromatography (SiO<sub>2</sub>, 10% MeOH/DCM) to give a pale yellow liquid Yield = 0.51g, 91% isolated yield.

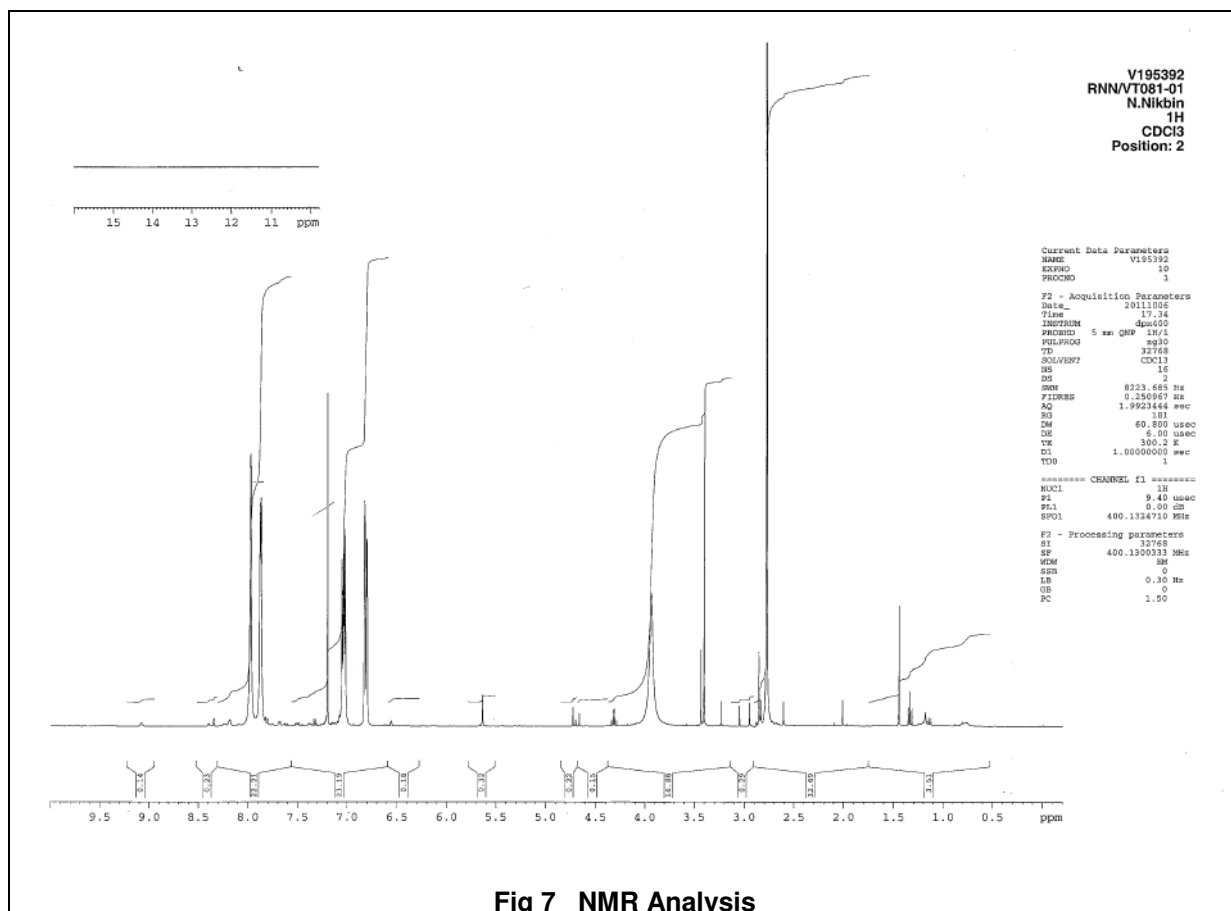
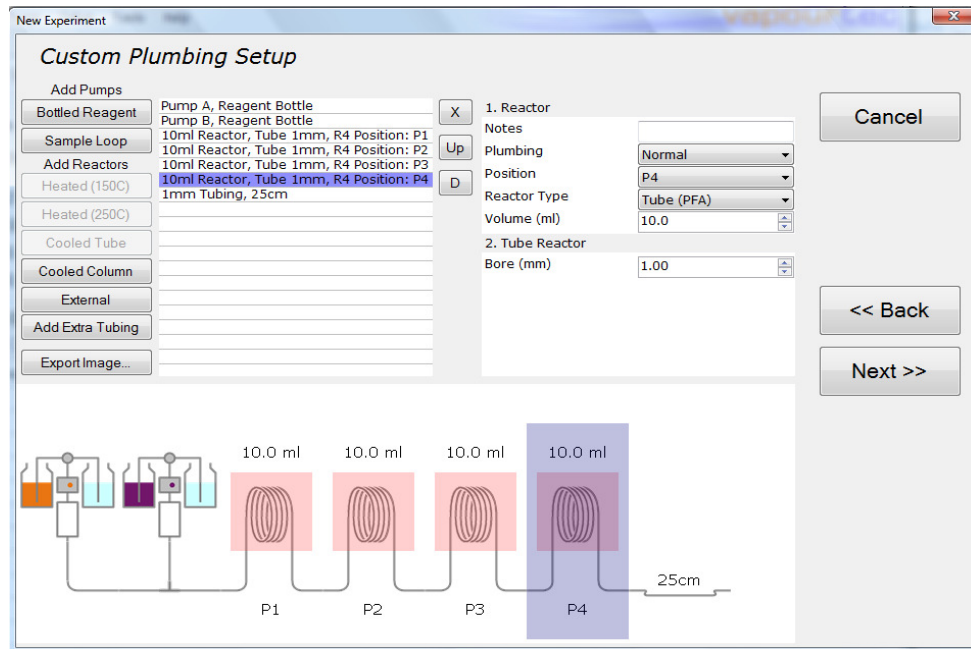


Fig 7 NMR Analysis

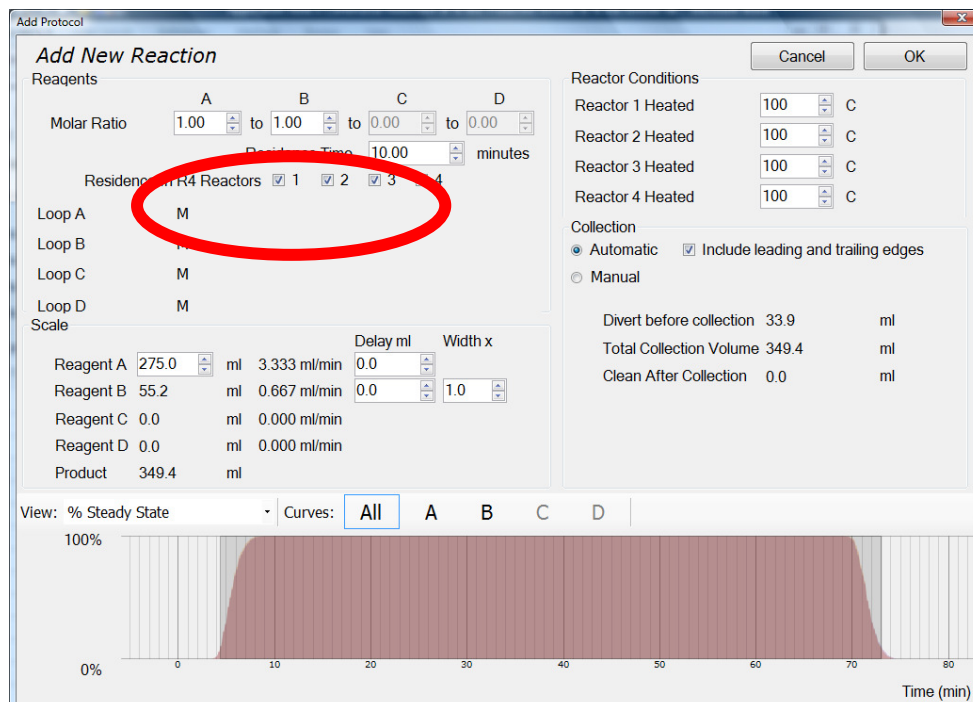
Extrapolating this experiment to continuous running. we can predict a mass transfer of ~1.0g/hr.

## Further Scaleup

As illustrated in Vapourtec application note 4 further scale-up can be achieved by connecting the maximum four tube reactors in series and applying the same reaction conditions (10min residence time, 100°C and 1.0eq of  $\text{LiAlH}_4$ ). This will theoretically achieve a mass transfer of 5.2g/hr at 91% yield.



Note that in this case the residence time should be specified to apply in total to all reactors





## **Conclusion**

This study shows how the Vapourtec R Series system can be used to optimise and scale-up reactions that would be difficult to scale in batch. Furthermore it shows how reactions using moisture sensitive reagents can be handled in a straightforward way (during optimisation and scaleup).

## **Acknowledgements**

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