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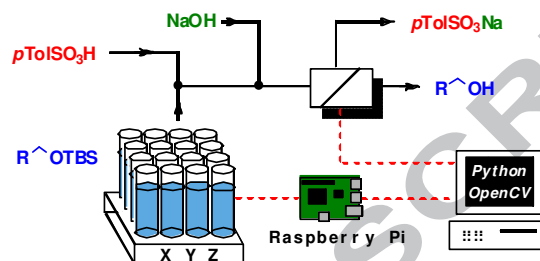
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Harnessing open-source technology for low cost automation in synthesis: flow chemical deprotection of silyl ethers using a homemade autosampling system

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Harnessing open-source technology for low-cost automation in synthesis: flow chemical deprotection of silyl ethers using a homemade autosampling system.

Matthew O'Brien^{a*}, Lisette Konings^{ab}, Matthew Martin^a and Jordan Heap^a

^a Lemnard-Jones Laboratories, School of Chemical and Physical Sciences, Keele University, Keele, Borough of Newcastle-under-Lyme, Staffordshire, UK, ST5 5BG.

^b Avans University of Applied Sciences, Lovensdijkstraat 61 – 63, 4818 AJ Breda, North Brabant, the Netherlands.

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ABSTRACT

An inexpensive homemade 3-axis autosampler was used to facilitate the automation of an acid catalysed flow chemical desilylation reaction. Harnessing open-source software technologies (Python, OpenCV), an automated computer-vision controlled liquid-liquid extraction step was used to provide effective inline purification. A Raspberry Pi single-board computer was employed to interface with the motors used in the autosampler and actuated fluidic valves.

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Introduction

In the last decade or so, flow chemistry has established itself as a promising alternative to more traditional batch synthesis approaches.¹ As only a small amount of material is being processed at any one time, this often confers significant safety benefits, particularly for transformations involving hazardous intermediates or conditions.² Additionally, due to the relatively small dimensions of the reaction and mixing zones, enhanced and well-defined surface-to-volume ratios often lead to superior interfacial mass and energy transfer,³ thereby facilitating efficient and scale-invariant processes. Opportunities for inline purification, for example using solid-supported scavengers and phase-switching protocols,⁴ are also an attractive feature of flow chemistry.

Flow chemical systems, incorporating many components which require numerical control (e.g. pumps, valves), naturally lend themselves to the use of electronic automation. A range of fully automated flow chemistry systems are now available from a number of commercial sources.⁵ However, whilst commercial automated synthesis platforms, of either batch or flow variety, are generally very well engineered, work 'out of the box' and provide robust operation, they are often relatively expensive (typically many tens of thousands of pounds) and this is a significant deterrent to many in the synthesis chemistry research community.

In addition to economic considerations, proprietary 'black box' platforms are somewhat difficult to customise and modify, with limited access to, and interoperability between, individual hardware and software components from different systems.

In a growing context of machine-assisted synthesis,⁶ where chemists are helping to drive technological innovation, we have been interested in harnessing emerging open-source hardware and software technologies to develop low cost automation systems for chemical synthesis.

Building on our recent work in the area of computer-vision controlled liquid-liquid extraction in automated continuous flow synthesis,⁷ we herein describe the utilisation of a low cost homemade autosampling system in the automated flow chemical deprotection of silyl ethers.

Silyl ethers are one of the most utilised groups for the protection of hydroxyl functional groups in chemical synthesis.⁸ A common deprotection protocol involves the use of catalytic acid in the presence of a nucleophilic alcohol, and we were interested in investigating a flow chemical variant of this transformation. The inclusion of an inline liquid-liquid extraction step to remove the acid would provide an inexpensive and convenient purification step and facilitate compatibility with further downstream processes. Whilst several groups have carried out continuous flow liquid-liquid extractions using expanded PTFE membranes to separate immiscible aqueous and organic flow streams,⁹ we have been interested in developing gravity-based separation systems¹⁰ for liquid-liquid extraction.

To this end, we constructed the flow system depicted schematically in Figure 1. We began investigations with *tert*-butyldimethylsilyl (3,4-dimethoxy)phenylethyl ether **1a** as the model substrate. The starting material and *p*TsOH solutions are introduced, *via* injection loops, into separate flow streams of DCM (both at 0.5 mL min⁻¹). The starting material is dissolved in

DCM whilst the *p*TsOH is dissolved in a 1:1 mixture of DCM and MeOH. When the reactant and acid streams mix at the T-junction, the resultant solution has a 3:1 ratio of DCM to MeOH. Experiments determined that a reaction loop of 20 mL (equating to a reaction time of 20 min) was sufficient to effect complete desilylation at room temperature (20-25 °C). These conditions were not optimised. It is likely that the use of higher temperatures and longer reaction times would permit the use of lower concentrations of *p*TsOH. In this study, we were particularly interested in testing the ability of the system to extract *p*TsOH, so these concentrations were appropriate for that purpose. Upon exiting the reaction loop, the flow stream is met by a stream of aqueous sodium hydroxide (0.3 M, 1.0 mL min⁻¹) which quenches the reaction and extracts the *p*TsOH as well as a significant amount of MeOH.

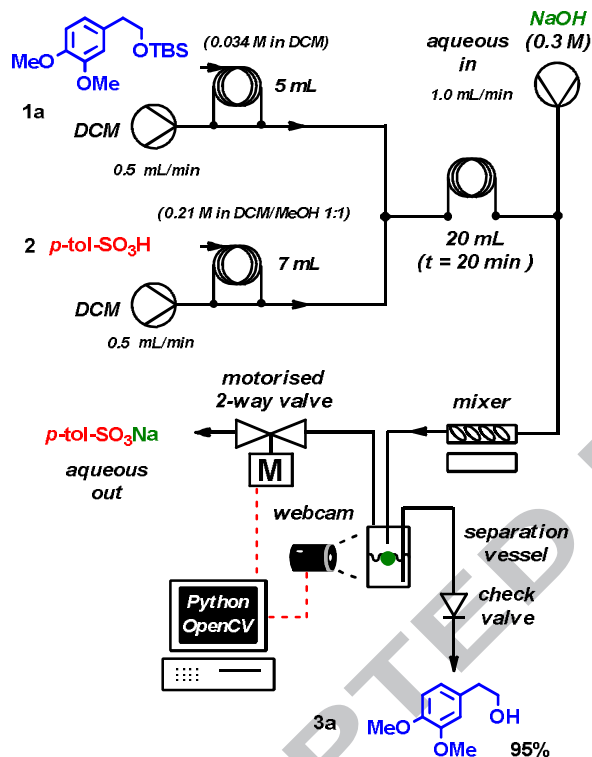


Figure 1. Apparatus schematic for flow chemical desilylation.

The inline mixer is a very simple and easily constructed device, consisting of several small PTFE coated magnetic stirrer bars placed in a glass omnifit column.¹¹ This sits on the plate of a magnetic stirrer-hotplate (stirring only, full speed) and ensures efficient mixing of the two phases. Upon leaving the mixer, the phases settle back into biphasic plug flow before entering the separation vessel. Here, the phases separate under gravity according to density and the DCM phase leaves the vessel through the lower exit whilst the lighter aqueous phase leaves through the upper exit. To ensure that the liquid-liquid interface remains within desired bounds, thereby preventing the flow streams from exiting through the wrong outlets, a coloured plastic 'float' which sits at the interface is monitored by a webcam connected to a computer-vision control system (Python,¹² OpenCV¹³). When the interface level falls below a set lower vertical level, the aqueous-out valve is opened, allowing liquid to leave *via* the upper exit causing the interface level to rise. When the interface level rises above a set upper vertical level the aqueous-out valve is closed, preventing liquid from

leaving through the upper exit. Liquid then leaves through the lower exit, causing the interface level to drop. The tube diameter for the upper exit is significantly wider than that for the lower exit, ensuring that the upper exit (when the valve is open) is the path of least resistance. The check valve, which may also provide a small amount of additional flow resistance, prevents any unwanted 'back-siphoning' of the organic outlet stream when the aqueous-out valve is open. The outlet from the system was collected for 60 min. The product, which was free of any *p*TsOH residue, as determined by ¹H and ¹³C NMR spectroscopy, was isolated in 95% yield simply by removing the solvent and silicon containing by-products under reduced pressure using a rotary evaporator followed by an Edwards vacuum pump (*tert*-butyldimethylsilyl methyl ether, the presumed major silyl by-product, is relatively volatile with a reported boiling point of 117 °C at atmospheric pressure¹⁴).

Having established suitable flow chemical conditions for the deprotection reaction, we sought to investigate its incorporation into an automated liquid-handling/reaction system we have recently been developing, comprising of homemade autosampling and valve-switching components.

The autosampling system is based around the 3-axis positional table shown in Figure 2. It resembles, and has a similar function to, the positional controller of a CNC mill or 3D printer. Indeed, the Cronin group have recently demonstrated the repurposing of a commercial 3D printer to add positional liquid dispensing functionality in an automated synthesis application.¹⁵ For our system, we were interested in building a device 'from scratch'.

The main design criteria for our 3-axis positional table were cost and ease of construction. In addition to the necessary components related to mechanical movement (e.g. stepper motors, bearing trucks) the principle construction materials were based on metric threaded rod (M5 and M8) and plastic 'corner blocks' which provide a convenient right-angled joint between the threaded rods. These materials, which are commonly used in the construction industry, are inexpensive and widely available.¹⁶

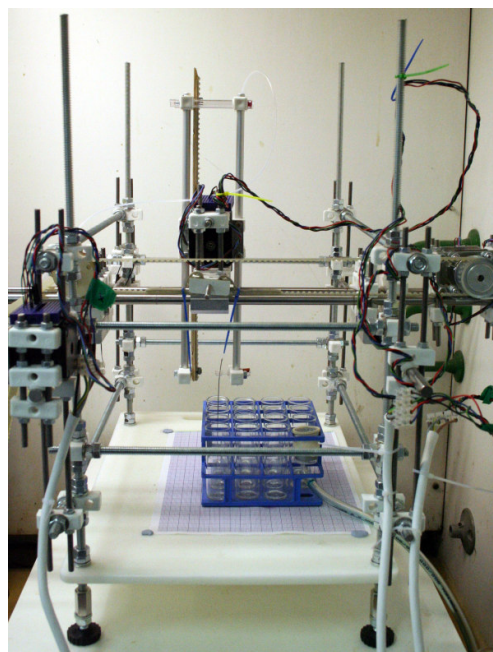


Figure 2. Homemade 3-axis autosampler.

Although we did not use 3D printers for the construction of any components, our design was very much inspired and informed by the vast body of work that has emerged from the open-source 3D printing movement, the Rep-Rap project¹⁷ in particular.

In addition to the autosampling unit, our system required the automation/actuation of three additional 3-way valves. This was accomplished using stepper motors, together with cheap flexible shaft couplings and inexpensive homemade mechanical attachments (as shown in Fig. 3).

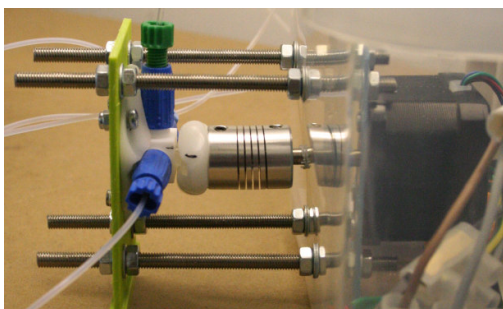


Figure 3. Mechanical coupling of stepper motor and 3-way valve.

We found the low temperature melt-processable thermoplastic polycaprolactam (a.k.a. ‘polymorph’ or ‘shapelock’) to be an invaluable material for creating rigid couplings between components with a variety of shapes. Further details and images of these couplings and the autosampling unit are provided in the ESI.

The entire automated flow system is depicted schematically in Figure 4. The aqueous-out valve, together with the 3-way valves and the 3 axis autosampler required a total of 7 stepper motors.

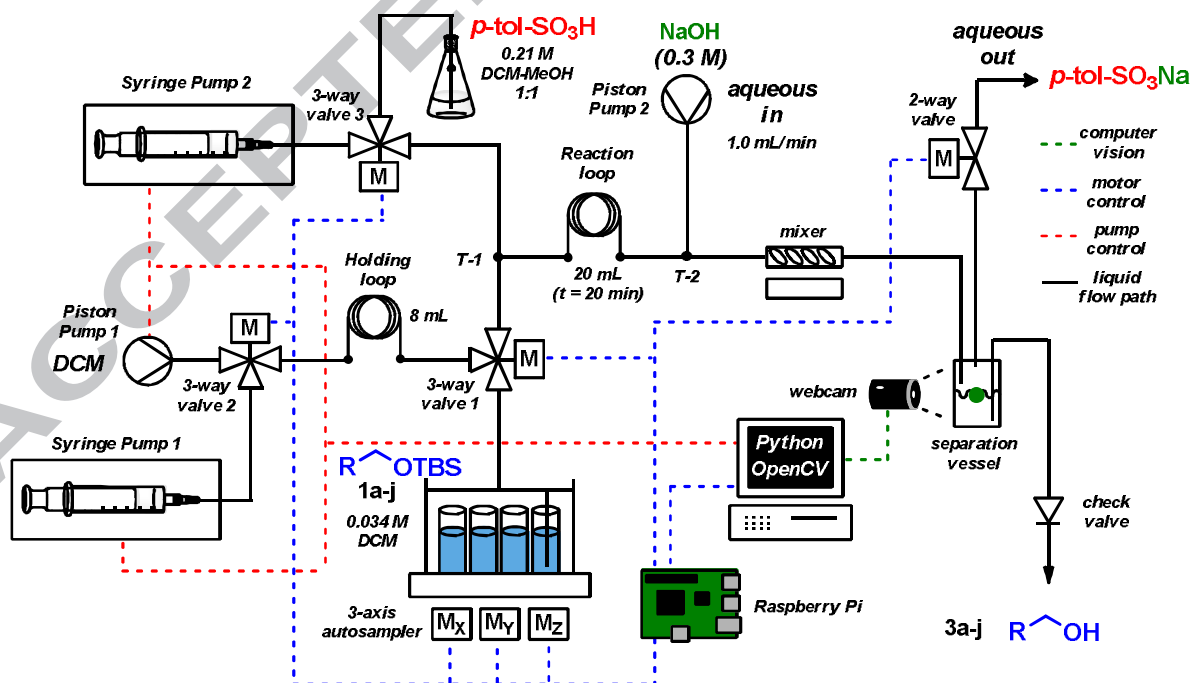


Figure 4. Schematic of automated flow system.

We opted for a configuration where the main Python/OpenCV control script incorporating the computer-vision control ran on a laptop computer which communicated through the serial/RS232 protocol (using the open-source PySerial library¹⁸) with the syringe pumps and piston pump 1 as well as to a secondary Raspberry Pi single-board computer responsible for controlling the motors *via* Pololu/Allegra A4988 motor driver boards.¹⁹ The complete source-code of the Python control scripts used in this work are provided in the ESI.

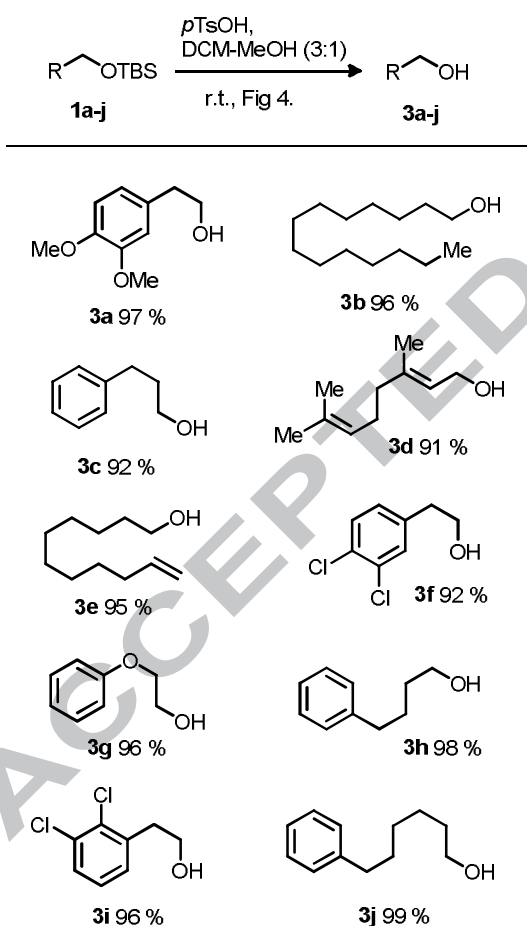
It is usually necessary, in 3D printers and CNC devices, to use microcontrollers for the control of stepper motors. This is due to the extremely accurate timing required to create precisely defined geometric tool paths. As our system did not require such critical temporal control, and could tolerate slight lags introduced by the operating system, we could use the Raspberry Pi to control the motor drivers directly.

The operation of the system is relatively straightforward. At the start of an automated run, the computer-vision system is initiated and then continues to control the aqueous-out valve for the duration of the run. The aqueous-in pump is set to pump at a constant rate of 1.0 mL min⁻¹.

Once the start command is given (by pressing ‘s’ on the computer keyboard), the autosampler reaction schedule begins. Initially, the 3-way valves are set so that syringe pump 1 is connected to the autosampler and syringe pump 2 is connected to the flask containing the *p*TsOH solution. Once the 3-axis autosampler has placed the needle in the correct vial of starting material solution, syringe pump 1, which is partly filled with dichloromethane, takes in the desired volume of liquid (5 mL). Of the 5 mL of substrate solution which is drawn up from the vial, 4 mL enters the 8 mL holding loop, partly filling it.

The tubing between the autosampler and 3-way-valve 1, which has a volume of 1 mL, holds the remaining solution; this is flushed out at the end of the cycle before moving to the next starting material. By using a holding loop with a volume in excess of the volume of substrate being used, syringe pump 1 is kept free of substrate. Once the holding loop has been loaded with substrate solution, syringe pump 2 takes in the desired quantity of the *p*TsOH solution (7 mL).

As the *p*TsOH reagent is common to every reaction, there is no need to use a holding loop to prevent cross contamination and the solution is able to enter the syringe which has been primed by partly filling with the *p*TsOH solution. The 3-way valves are now switched so that the holding loop is connected upstream to the piston pump and downstream to T-junction T-1, whilst syringe pump 2 is also connected to T-1. Syringe pump 2 then begins to dispense the *p*TsOH solution (at 0.5 mL min⁻¹). After 30 seconds, piston pump 1 begins pumping DCM (also at 0.5 mL min⁻¹). The 4 mL plug of starting material in the holding loop meets the stream of *p*TsOH at T-1 before the combined reaction stream enters the reaction loop. At a combined flow rate of 1.0 mL min⁻¹, the volume of the reaction loop (20 mL) corresponds to a reaction time of 20 min.



Scheme 1. Results of automated flow desilylation

Syringe pump 2 dispenses 7 mL of the *p*TsOH solution, commencing 30 seconds before piston-pump 1 begins pumping the substrate solution out of the holding loop. This results in a

0.25 mL 'overlap' of the *p*TsOH solution before the front of the substrate plug and a 2.75 mL overlap at the tail, ensuring that the substrate is always accompanied by the *p*TsOH solution. Once syringe pump 2 has dispensed 7 mL of the *p*TsOH solution, it stops and the speed of piston pump 1 is increased to 1.0 mL min⁻¹, maintaining a 1.0 mL min⁻¹ overall flow rate through the reaction loop. Piston pump 1 continues to pump DCM through the system for a further 60 min, during which time the organic outlet stream is collected. After this time, piston pump 1 stops pumping, the valves are switched to their initial positions and the autosampler moves the needle to the waste position. Syringe pump 1 then dispenses 5 mL of DCM, returning it to its original state and also flushing the residual substrate solution from the tubing between the autosampler and 3-way-valve 1. The autosampler then moves the needle to the next substrate vial and the process begins again. An animated schematic diagram, illustrating the operation of the system upstream of the liquid-liquid extraction step is included in the ESI. It should be noted that, in this configuration, the product collection flasks were changed manually. We are currently working on upgrading the system so that the autosampler also performs the switching between collection vessels. A total of 10 different *tert*-butyldimethylsilyl ethers (Scheme 1) were deprotected in a single automated run. The free hydroxyl products were isolated in excellent yield and high purity simply by removal of the solvent and silicon containing by-products under reduced pressure. No cross contamination was observed between the products. The ¹H, ¹³C and DEPT-135 NMR spectra of all silyl ethers and deprotection products are provided in the ESI.

Conclusions

A homemade 3-axis autosampler, constructed using inexpensive and readily available materials, was used in the automated flow chemical deprotection of a series of *tert*-butyldimethylsilyl ethers. The hydroxyl products were formed in high yields and with excellent levels of purity due to the incorporation of a computer vision controlled liquid-liquid extraction step. The control script (the source-code of which is provided in the ESI) was written using a number of freely available open-source software components (e.g. Python, OpenCV, PySerial). We are currently investigating the use of this system in a range of synthetic chemistry applications. We are also aiming to improve and expand upon the functionality of the system and will report our findings in due course.

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An home-made 3-axis autosampler was used to provide low-cost automation in a series of flow chemical desilylation reactions.

System control was achieved using a number of open-source software components (Python, OpenCV, PySerial).

A Raspberry Pi single-board-computer was used to provide an interface to the electronic hardware components.

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