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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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

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separate immiscible aqueous and organic flow streams,[9] we have been interested in developing gravity-based separation systems[10] for liquid-liquid extraction.

To this end, we constructed the flow system depicted schematically in Fig. 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.

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] OpenCV[13]). 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 ^{1}H and ^{13}C 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 pressure[14]).

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 Fig. 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
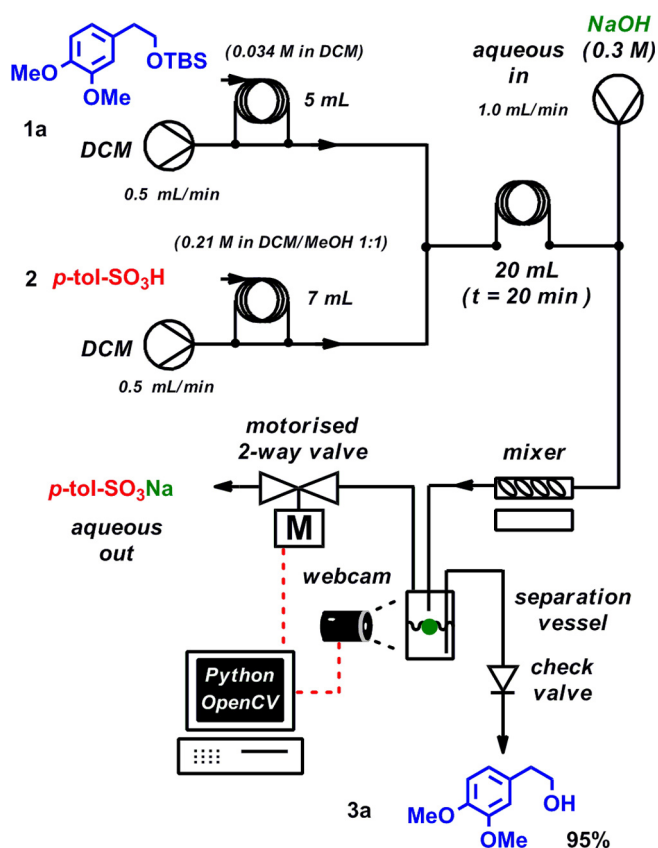

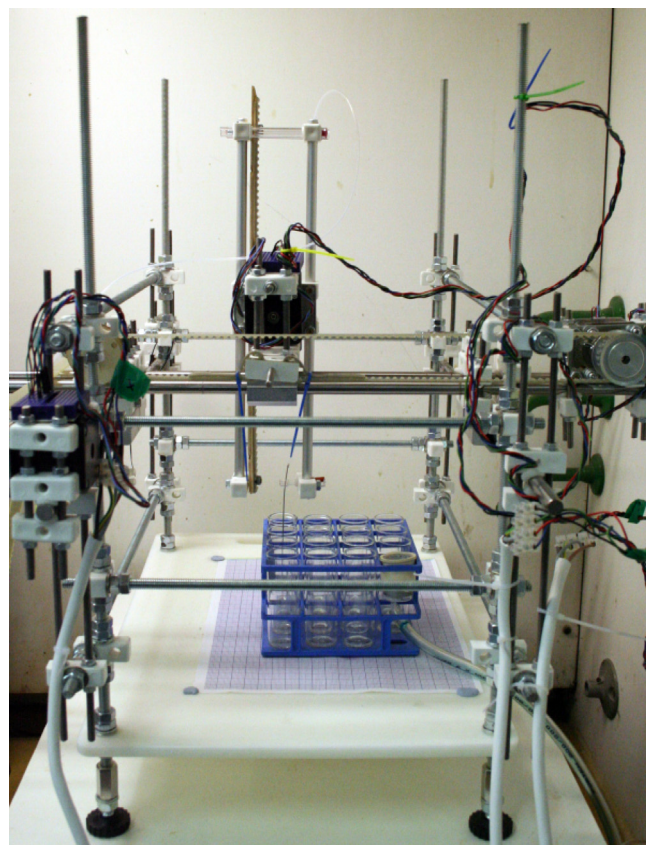**Fig. 1.** Apparatus schematic for flow chemical desilylation.

Fig. 2. Homemade 3-axis autosampler.