Autonomous Execution of Highly Reactive Chemical Transformations in the Schlenkputer

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We demonstrate how it is possible to design a modular programmable inert-atmosphere *Schlenkputer* (Schlenk-line-computer) for the synthesis and manipulation of the most highly reactive compounds including those which are air- and moisture sensitive or pyrophoric. To do this we have designed and built a programmable Schlenk Line using the Chemputer architecture for the inertization of glassware which can achieve a vacuum line pressure of 1.5×10^{-3} mbar and integrated a range of automated Schlenk glassware for the handling, storage, and isolation of reactive compounds at sub ppm levels of O_2 and H_2O. Utilising this hardware in conjunction with our platform has allowed the automation of a range of common organometallic reaction types for the synthesis of four highly reactive compounds from across the periodic table: $[Cp_2Ti^{III}(MeCN)_2]^+$ [1], $Ce^{III}\{N(SiMe_3)_2\}_3$ [2], $B(C_6F_5)_3$ [3] and $\{^{Dipp}NacNacMg^{I}\}_2$ [4] which are variously sensitive to temperature, pressure, water and oxygen. Automated purification by crystallisation, filtration and sublimation are each demonstrated along with analysis using inline NMR or reaction sampling for UV/Vis. Finally, we demonstrate automated ultra-low temperature reactivity, down to −90 °C as well as safe handling and quenching of alkali metal reagents, using dynamic feedback from an *in-situ* temperature probe.

Keywords: Schlenk, air-sensitive, inert-atmosphere, automation, digital chemistry.

Automated systems for chemical synthesis, discovery and prediction have potential to revolutionise the chemical sciences.[1] Bespoke equipment such as peptide synthesisers and preparative HPLC reduce the

level of training, time and discipline specific skill required for routine tasks and increasing safety by minimising human contact with toxic reagents. Building on these advances recently there has been a drive towards more 'universal' synthesis machines which can undertake more of the operations automatically with minimal labour costs.[2-4] Current chemical automation technologies focus strongly on aerobic transformations, often using liquid handling (LH) systems for low to medium scale synthesis. Whilst some of these systems incorporate basic inert atmosphere conditions control, these are normally rudimentary, are not programmable since they only can purge or blanket the system with inert gas. As such these approaches are inadequate for the majority of robust organometallic or air-sensitive chemistries which must be conducted at sub ppm levels of O_2 and H_2O.[5,6,7] Similarly, reactions under controlled gas environments (e.g. CO, X_2 etc) are not remotely operable despite the safety concerns for manual handling. This means the use of automation at the forefront of highly reactive chemistry is severely underdeveloped.[8,9]

Manual inert and controlled atmosphere chemistry has, on the other hand, developed hugely in the past 50 years due to the increasing availability of technologies such as positive-pressure gloveboxes, Schlenk lines and solvent purification systems.[10-13] In tandem our ability to investigate and exploit species which hydrolyse or oxidise readily under atmospheric conditions has expanded rapidly. However, the manipulation of reactions under inert conditions still requires significant specialist training[14] and many procedures fail due to poor technique.[15] In addition, with manual handling it is significantly more challenging to carry out multiple inert reactions at one time limiting the number of new compounds which can be made, or the chemical space explored, meaning organometallic chemistry currently moves at a slower pace than its aerobic counterparts.[16] Several key features delineate inert-atmosphere chemistry from traditional bench techniques. Firstly, removal of air from the flasks and system in question by

application of vacuum is required.[17,18] This is typically achieved using Schlenk glassware which has a manually sealable gas handling side arm. Reduced pressure of at least <0.1 mbar is required for the most sensitive chemistry to reduce the levels of O_2 and H_2O to sub ppm quantities. This effect is carried out using a Schlenk line or Inert Manifold which has two distinct lines, one for vacuum and one for inert gas, and several sets of taps which allow connection to the reactors or glassware in question. After evacuation and refill in triplicate (often known as cycling or inertization), to reduce remaining air to adequate levels the flasks can be maintained under positive pressure throughout a reaction by retaining connection to the inert gas line on the manifold.

Herein, we report the design, development, and deployment of the first fully automated controlled-atmosphere synthesis robot known as the Schlenkputer, which can reach reduced pressures of 1.5×10^{-3} mbar and allows for automated inertization of reactor flasks; a range of key glassware allowing for the gas tight sealing of the flask for the duration of our experiments; and the coupling of this inert-gas handling system with a liquid handling backbone Chemputer,[2,5] see Fig. 1. Using this new system we demonstrate the complete automated synthesis of a range of sensitive compounds from across the periodic table including: the colorimetric indicator $Cp_2Ti^{III}(MeCN)_2$ [1], readily oxidisable $Ce^{III}\{N(SiMe_3)_2\}_3$ [2], highly moisture sensitive $B(C_6F_5)_3$ [3] and the alkali metal-reduced $\{DippNacNacMgI\}_2$ [4]. Through the use of our Chemical Programming language (XDL)[19] we are able to remotely program and conduct the synthesis, sampling and analysis of an entire reaction process whilst maintaining inert conditions. In addition, we demonstrate the incorporation of in-line NMR spectroscopy, temperature sensing for safe quenching of alkali metal reagents, and reaction sampling for UV/vis analysis.

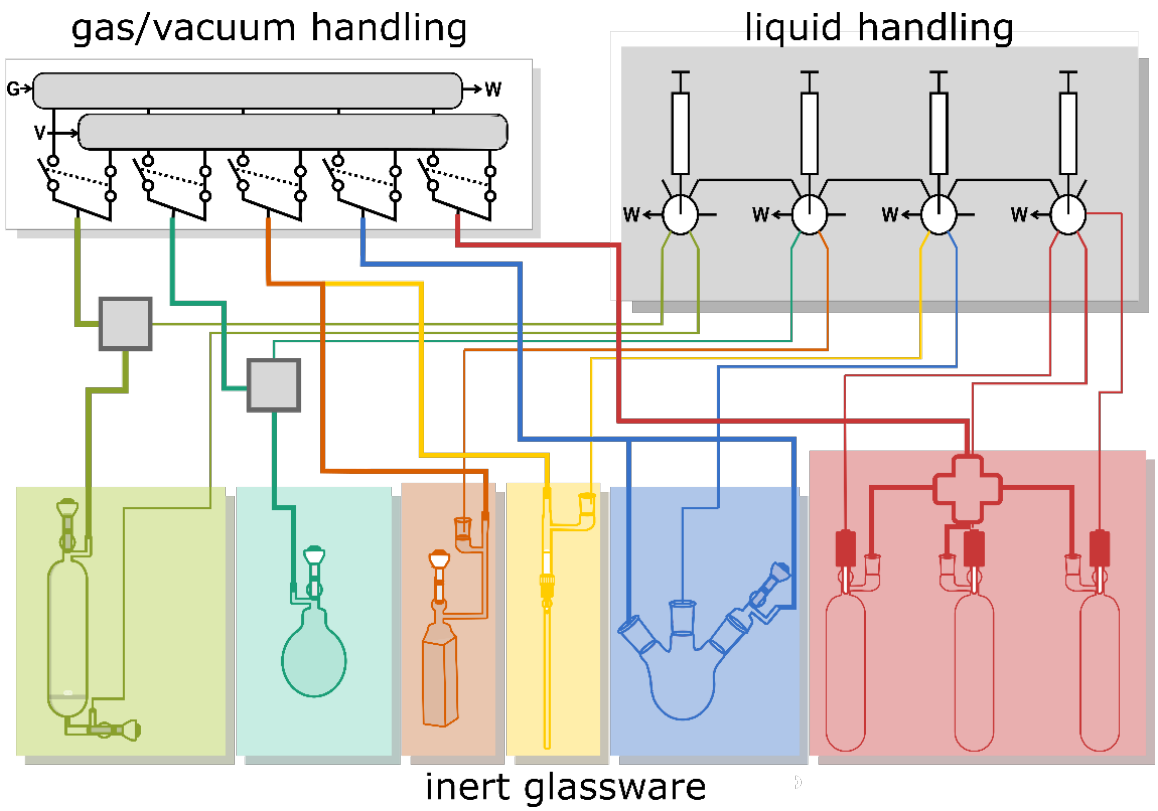


Fig. 1 Overview of the Schlenkputer. The Schlenkputer combines automated liquid handling and gas handling systems in one platform. Route map shows the liquid handling connections (thin lines) between the Chemputer backbone and reactors as well as gas/vacuum handling connections (thicker lines) between the inert manifold and the bespoke glassware designed in this work (left to right: Schlenk filter flask, green; Schlenk collection ampoule, teal; sealable UV/vis cuvette, orange; J Young NMR tube adaptor, yellow; 3-necked RBF appended with remotely operable tap, blue; Solvent storage ampoules with inert gas flow splitter, red). (G: Inert gas inlet; V: vacuum inlet; W: waste outlet).

Schlenkputer Hardware. An inert manifold (Schlenk line) consists of an array of taps connecting two gas/vacuum lines to tubing for connection to various flasks and reactors. To allow for flexibility in conducting manipulations each tap must be independently operable. Two common Schlenk line tap designs exist: double oblique taps which are rotated to provide a connection between the reactor and the respective manifold lines; or a pair of greaseless stopcocks (J Young®, Rotaflo® etc) which individually open the reactor to either the vacuum or gas line (or potentially even both if improperly used). In our work we elected to design a manifold based on the latter style with 5 reactor lines thus using 10 vacuum

taps (i.e., 5 pairs).[20] These vacuum taps can be linearly actuated by application of a weak positive or negative pressure (*ca* 50 mbar) to the hollow of the glass barrel, see Fig. 2A. Three FFKM O-rings provide a tight seal within the barrel towards the atmosphere with the terminal O-ring acting to open or close the system to the reactor depending upon the linear position of the barrel.

Control over the actuation of these taps was provided by utilising a programmable solenoid manifold consisting of 12 electromagnetic valves connected to a diaphragm pump and gas lines which when engaged were able to affect the opening and closing of each of these taps individually, see SI Section 3.2. Our Schlenkputer line, when coupled to a rotary vane pump can achieve ca 1.5×10^{-3} mbar pressures and withstand at least 1 bar positive pressure of inert gas, see Fig. 2B. Using the combination of this technology the taps can be controlled using direct XDL commands such as "`SchlenkLineOpenVacuum`" (Fig. 2C) or these commands can be integrated to allow the use of high-level unit operations within the XDL file such as "`EvacuateAndRefill`" whereby the line is cycled automatically between opening the flask to the vacuum line and the gas line. In each case the length of time, cycle repeats and specific flask can be input as parameters with 3 mins vacuum, 2 mins gas and 3 repeats found to be optimal for inertization in our hands.

Development of Automated Sealable Glassware for Inert Atmosphere Chemistry. In classical Schlenk chemistry, flasks are commonly opened under a flow of inert gas to allow the insertion of a cannula, usually through septa, for liquid transfer.[17,18] However, the Chemputer liquid handling backbone does not require opening and closing during a reaction and as such, our inert atmosphere syntheses can in large part be carried out using commercial Quickfit® glassware such as round bottomed flasks. Despite this there is still a need to utilise automated Schlenk-type flasks in key places where sensitive reagents

or reactants must be retrieved from a glovebox, where reactive products must be isolated as solids, or where the reactive species must be stored for long periods e.g., during crystallisation. In addition, there are some operations for which direct opening and closing of connections between one reactor and another may be required.

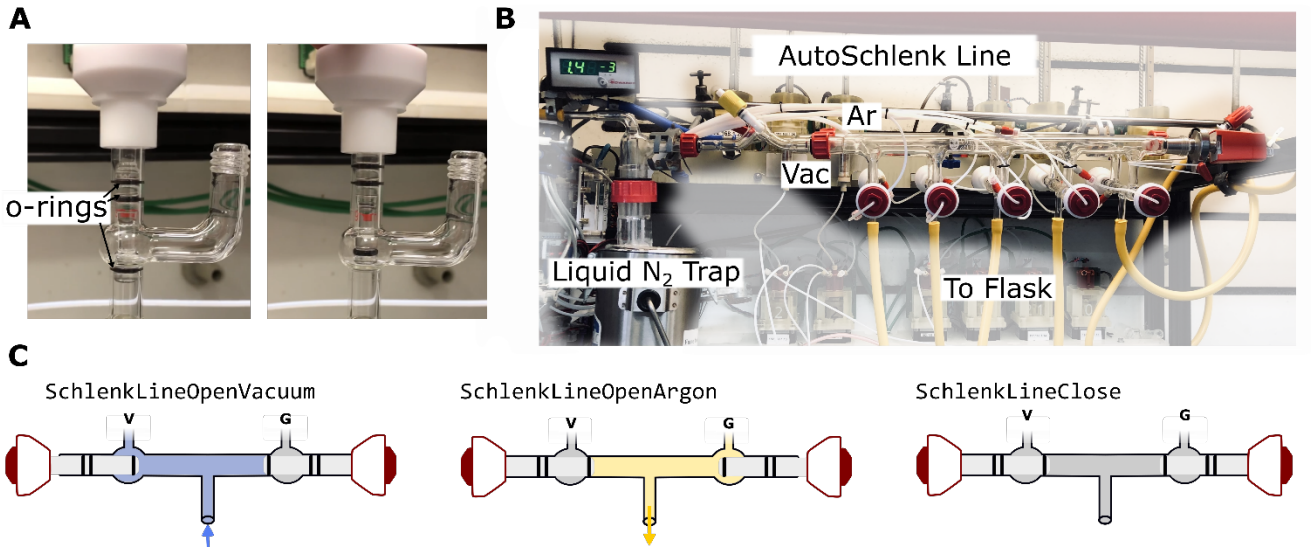


Fig. 2 AutoSchlenk hardware. (**A**) Remotely operable vacuum taps open and close by application of a negative pressure to the hollow of the glass tap. (**B**) Using these taps a remotely-operable, automated Schlenk line has been constructed which allows for the application of high vacuum (ca 1.5×10^{-3} mbar) and high pressure N_2/Argon (ca 1 bar) to reaction flasks. (**C**) Chemical programming language commands have been developed to operate these taps.

For these reasons we developed a set of key pieces of glassware to facilitate the full automation of our reactions, see Fig. 1, Fig. 3A. Each flask utilises the same remotely operable taps as the Schlenk line and is automatically controlled in a similar way. Chemically inert FFKM O-rings provide minimal swelling upon chemical or solvent exposure resisting at least 48 h submersion in solvent without loss of function. Firstly, an isolation flask was developed for collection of pure material, see Fig. 3A left. A 250 mL RBF with a single automated tap was designed and built. Solutions of product materials may be transferred into this flask through the liquid handling system and the solvent removed *in vacuo* allowing the solid

material to be extracted in an inert atmosphere glovebox. Next a filtration flask, see Fig. 3A right, was produced, allowing separate inlet and outlet ports for isolation of solid material. The large volume allows crystallisation of the product in the flask or alternatively filtration through celite to remove particulate material. Finally, a single tap was appended to a Quickfit® joint for flexible use of a remotely operable tap connected to a standard RBF, see Fig.7E. This tap can be used to control the evaporation of solvent/reagents into an external cryogenic trap (for example in the Cerium(III) silylamide synthesis, below). The XDL commands `SchlenkFlaskTapOpen` and `SchlenkFlaskTapClose` were designed for use with any of this glassware. Up to two taps can be used in conjunction with the Schlenk line based on our current design.

Integration of the automated Schlenk line with liquid handling. Two different methods have been utilised for the integration of the gas handling system with the liquid handling backbone of the Chemputer. The simplest involves the use of multi-necked glassware fitted with both a liquid handling adaptor (B19 to GL14 adaptor for 1/8" LH tubing) and a gas/vacuum adaptor (B24 to 1/4 in. glass hose barb). However, this option does not allow for the facile, automated sealing of the vessel for transport to a glovebox or storage. The Schlenkputer glassware set we have described above (Fig. 3A) has been designed with only one inlet/outlet per tap (neck). For integration with these flasks a tube-in-tube strategy was designed to allow both inertization and liquid handling through a single port (Fig. 3B & S43).

A route-map style depiction of the integration of the hardware described herein with the previously reported liquid handling system of the Chemputer is shown in Fig. 1. Here, the solvent storage flasks, Fig. 1 pink, are connected to the Schlenkputer through a gas line splitter (Fig. S42) which means one manifold line can provide all the required solvents with a gas blanket. The Schlenk Filter Flask (Fig. 1

green, Fig. 3A right) described above is connected through a Tube-in-Tube adaptor on the top port but directly to liquid handling on the bottom while the Schlenk collection Flask (Fig. 1 teal, Fig. 3A left) only requires a single inlet position to transfer liquids in and to remove the solvents, allowing for collection of the solid reaction product. We have also designed a UV/vis cuvette (Fig. 1 orange, Fig. 6C) and J Young® tap NMR tube adaptor (Fig. 1 yellow) for our system to facilitate sampling during and after reactions. Finally, the alternate method of using a standard QuickFit® RBF allows for different necks to be connected to the liquid and gas handling manifolds respectively (Fig. 1 blue). The outlet port of the inert gas line on the Schlenkputer runs through the waste collection bottle and to a bubbler (Fig. S34). This line can also be split to allow an inert gas flow over subasealed reagent bottles such as nBuLi.

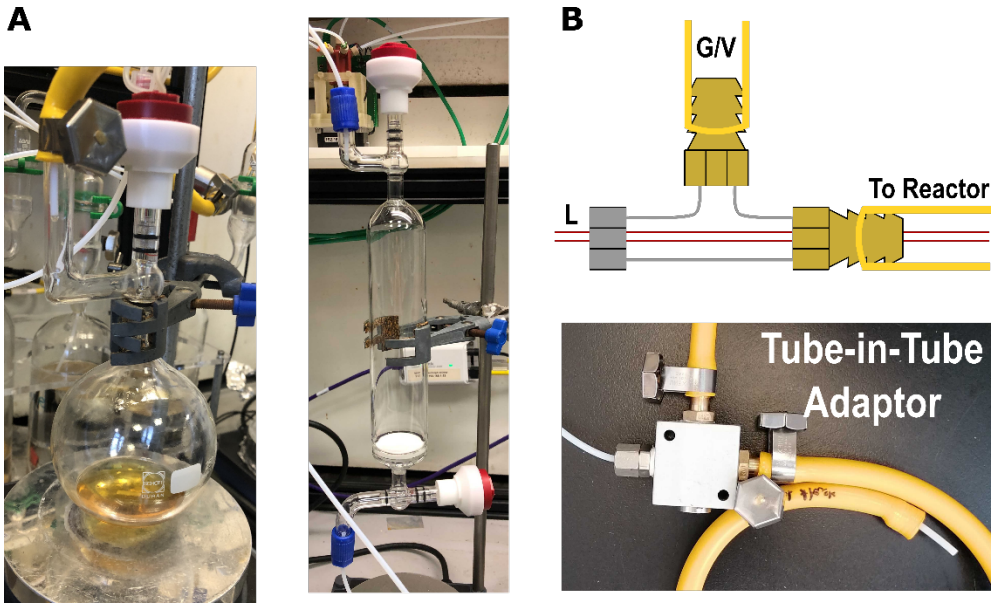


Fig. 3 Schlenkputer hardware for product isolation. (A) Glassware for the Schlenkputer system including an inert atmosphere isolation flask and inert atmosphere filter flask; **(B)** The tube-in-tube adaptor system which allows liquid and gas handling through one flask port.

This method has several advantages: first, these tube-in-tube adaptors can allow for connection of the inert manifold to liquid handling systems which are not designed with inertization in mind or allow the

use of non-bespoke glassware; secondly, the adaptors can be connected in a daisy chain fashion thus making optimal use of the five manifold lines of the Schlenkputer; this setup also provides an additional safety feature for the handling of pyrophorics since any potential leaks in the LH tubing will only expose the system to inert gas rather than air.

Periodic Table Flight Having designed a programmable hardware and software system for inert atmosphere synthesis four sensitive compounds from across the periodic table were chosen to develop the Schlenkputer implementation focussing on control, reliability, safety, and interoperability. Each has a different sensitivity profile with some sensitive to oxygen, others moisture, as well as temperature and vacuum, see Fig. 4.

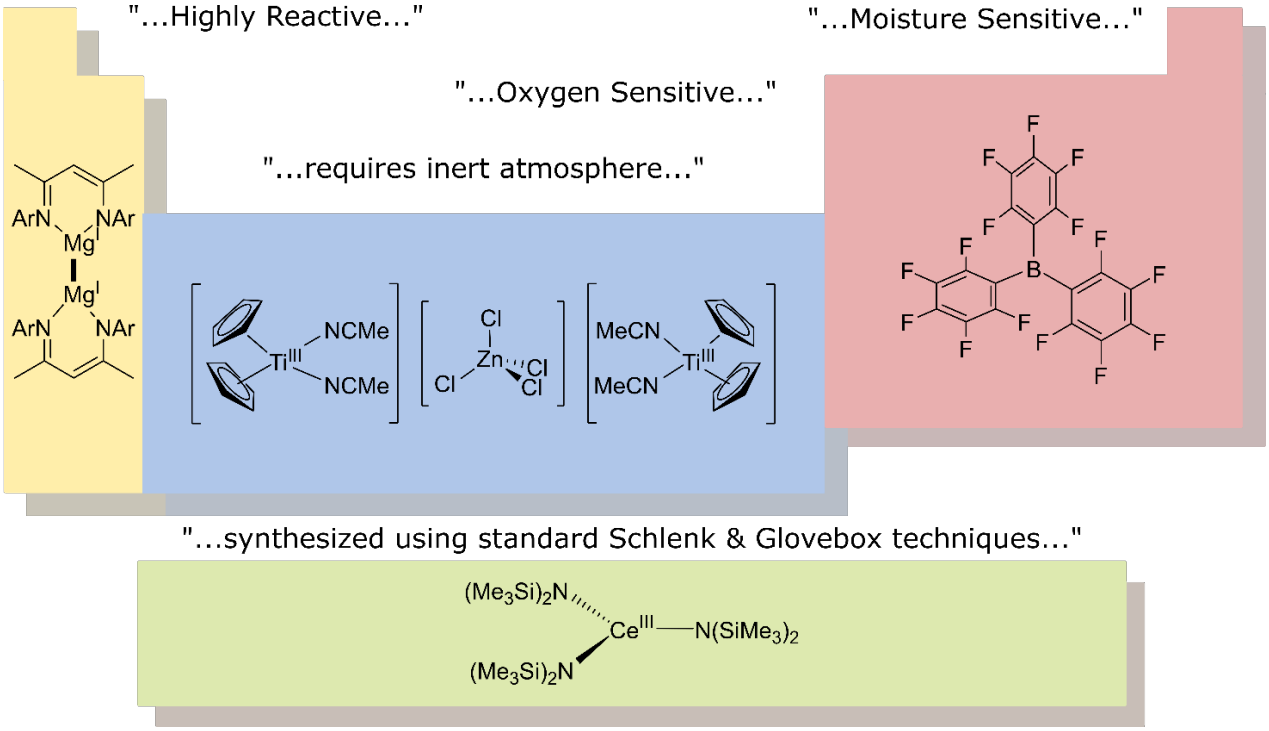


Fig. 4 Periodic table flight. Highly sensitive compounds can be found from around the periodic table. For our purposes a single compound from each block was chosen to demonstrate the versatility of the Schlenkputer. S-block: $[(^{Dipp}NacNac)Mg]_2$, yellow; d-block: $[Cp_2Ti^{III}(MeCN)_2]_2[ZnCl_4]$, blue; p-block: $B(C_6F_5)_3$, pink; f-block: $Ce^{III}(N(SiMe_3)_2)_3$, green.

d-block complex – Titanocene. All known automated chemical systems exploit liquid handling (LH) pumps and valves in concert with reactors or flow loops to undertake the operations required for synthesis. For reactions involving highly sensitive reagents it is key that not only the reactor is inertized but that the entire system is free from oxygen and moisture thus strategies to fully inertize the LH system were investigated using $[Cp_2Ti^{III}(MeCN)_2]^+$. The titanocene species $[Cp_2Ti^{III}(MeCN)_2]^+$ is one of the most widely used colorimetric indicators,[21,22] turning from blue to yellow readily upon exposure to oxygen. In the first instance this reaction afforded us the opportunity to gain rapid feedback on our ability to exclude air from the pump-valve liquid handling system of the Chemputer. By transferring the blue solution through the sets of valves and pumps we could identify areas where simple cycling of the reactor flask was insufficient for an entire synthetic procedure.

We immediately identified the connections between the valves and pumps as well as the connections between individual valves as being 'dead' areas where out Schlenkputer line was unable to purge, see Fig. 5A. As such when transferring the blue titanocene solution between valves rapid decolourisation was observed. To address this, we adopted two complementary approaches which can both be used to inertize liquid handling systems: 1) When inertizing a reactor flask the liquid handling tubing connecting the glassware and the valve was naturally evacuated since it was open to the flask. By also turning the valve to the appropriate reactor position to open the connection between the pump and the flask before inertization we were able to remove air from these lines (Fig. 5A, yellow). 2) Removing air from the connection between valves (Fig. 5A, green) was more challenging since, in our system, these could not be directly connected to the flask and thus to the Schlenk line. Instead, these short tubes were purged by transferring dry solvent through the full liquid handling backbone in triplicate. With these measures in

place both the flasks and liquid handling system were demonstrated to be free from oxygen by repeated transfer of the colorimetric indicator throughout the system (Fig. 5C).

The synthetic protocol for the synthesis of $[Cp_2Ti^{III}(MeCN)_2]^+$ involves the suspension of the air stable bis(cyclopentadienyl)titanium(IV)chloride in acetonitrile followed by reduction over solid Zinc dust (Fig. 5B). During the reduction the red solution turns first green, then deep royal blue in the absence of air however oxygen exposure results in rapid decolourisation. In order to achieve the automated synthesis and isolation of the product in this case the reaction was setup to involve two RBFs and one crystallisation (Schlenk) flask (Fig. 3A). Each RBF was charged with one of the solid reagents (Cp_2TiCl_2 or Zn dust). The automated procedure prompts the user to charge the flask at the appropriate time (i.e., once the flask has cooled) and when addition has been confirmed the automated run continues. This 'cobotic' or cooperative robotic strategy means the reaction setup is guided and assisted by automation, but the reaction process is fully automated after run setup which takes approx. 15-20 mins (Fig's 5E-F). Remote notification steps which send a Slack message to the users phone or desktop can also be added for hazardous processes or where the user would like to observe a portion of the reaction.

The Cp_2TiCl_2 is then dissolved in acetonitrile before the red solution is transferred to the Zn containing flask with stirring for 30 mins. The resultant blue solution is transferred through the liquid handling backbone to the Schlenk Flask whereupon the upper tap has been automatically opened. Next the Schlenk Flask is charged with dry Et_2O and the flask sealed for 48-72 h during which time the solution remained deep blue. Finally, the bottom tap on the Schlenk flask is opened to pump out the mother liquor and yield the crystalline product on the Schlenk Flask filter frit. These crystals can be isolated for XRD analysis by pumping Fomblin Y oil automatically into the Schlenk Flask, thus providing some protection from

air upon retrieval of the crystals. In our case XRD analysis demonstrated the formation of the target compound by comparison with published structures (Fig. 5D).

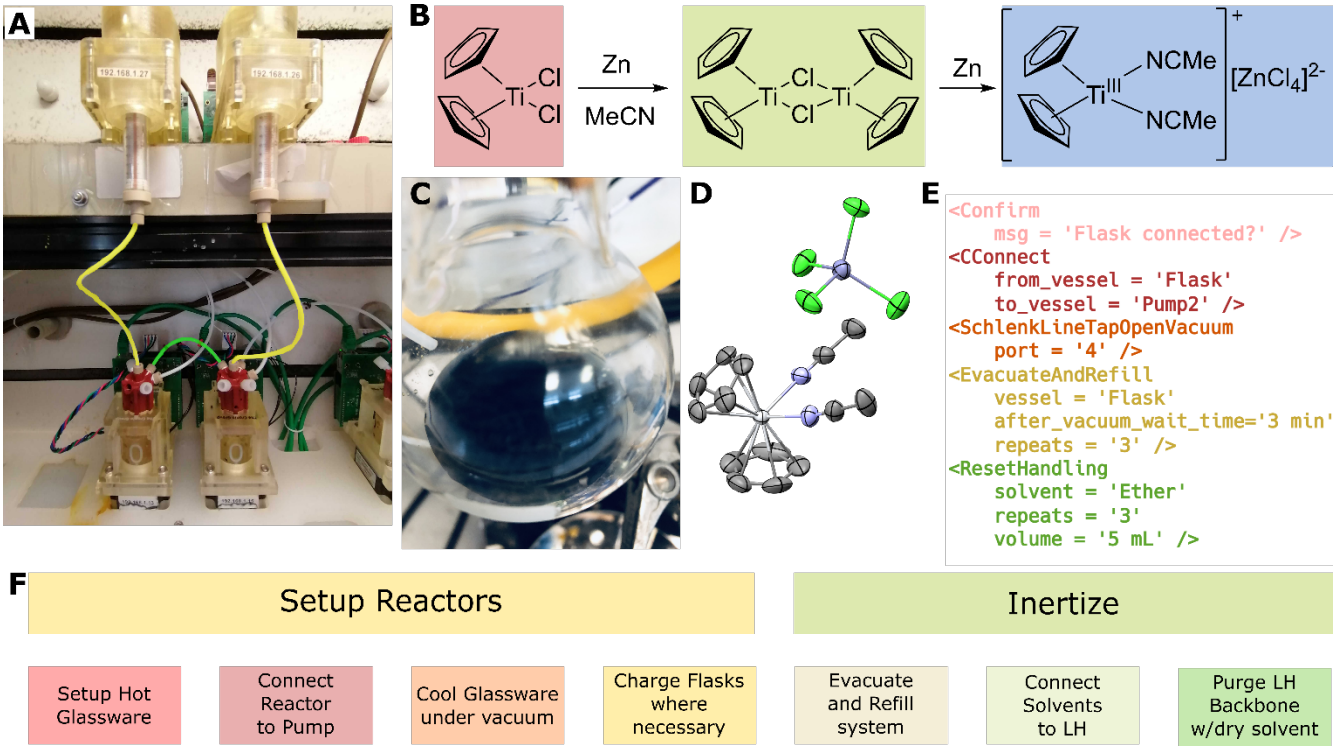


Fig. 5 | Synthesis of colorimetric indicator titanocene(III). (A) Photograph of part of the Schlenkputer liquid handling backbone with Valve-Pump and Valve-Valve "dead" areas highlighted (yellow & green respectively). **(B)** Scheme showing Ti(IV) reduction with indicative solutions colours for different stages. (C) Colour of the product solution after passing through the fully inertized LH backbone. **(D)** XRD Crystal structure of isolated product from automated reaction. **(E)** Section of a XDL procedure showing the process of connecting and inertizing a flask and the liquid handling system. **(F)** Overview of the guided (semi-automated) reaction/platform setup process.

f-block complex – Luminescent Cerium silylamide. Lanthanide coordination chemistry is another field which relies upon inert-atmosphere techniques.[23,24] Whilst most lanthanides exist almost exclusively in the 3+ oxidation state Cerium is one of the few which, in addition to undergoing rapid ligand hydrolysis, is readily oxidised in air to Ce(IV) owing to its position within the 4f block. In our next experiment we

targeted a widely used cerium amide which has been previously shown to exhibit luminescent properties, but which can also act as a precursor for a wide range of novel lanthanide species.[25] For inert and anhydrous chemistry on salts to succeed it is vital that the precursors reagents are free from water coordination, as in the titanium example above. However, electropositive metals such as those of the f-block are highly hygroscopic yielding very stable hydrated species rapidly in air. The reagents required to dehydrate metal salts (e.g. HX acids, $SOCl_2$, TMSCl and Tf_2O) are often highly corrosive, and could be detrimental to our automated systems, therefore, our ability to automate the handling of these compounds was investigated.

Addition of excess neat triflic acid to an aqueous suspension of $Ce_3(CO_3)_2$ was undertaken using the liquid handling backbone of the Schlenkputer under air (Fig. 6A). The resulting acid suspension was first refluxed (100 °C) in an RBF connected through a Findenser^{TM} to the Schlenkputer bubbler. This allowed us to investigate the effect of the acid on both the liquid handling hardware and the Schlenkputer O-rings. Visual inspection showed no impact of either the liquid transfer or refluxing of the acid solution. After automated workup, IR Analysis demonstrated that the resulting $CeOTf_3$ was free of hydration by the absence of the key -OH band at *ca* 1650 cm^{-1} (*cf.* 1657 cm^{-1} in $CeOTf_3.xH_2O$, See SI Fig. S10).[26]

Our adapted literature procedure[27] for the synthesis of $Ce(N(SiMe_3)_2)_3$ consisted of the salt metathesis reaction of anhydrous $Ce(OTf)_3$ with $KN(SiMe_3)_2$ (KN") in THF, yielding highly soluble CeN"$_3$ as a yellow solid. Replacement of the THF solvent with hexane, by evaporation under reduced pressure is a key step in the isolation the highly soluble product from solvated side products. In organic chemistry a rotary evaporator may be automated to allow for removal of solvent,[2,5] however, the pressure obtainable in these systems is usually insufficient to obtain a robustly inert system meaning an alternate solvent

removal route is required for the Schlenkputer. After mixing of THF solutions of the cerium salt and silylamide base the solvent was removed by connection of our automatically controllable side arm to a cryogenic trap which was maintained under dynamic vacuum, using the Schlenkputer, for 16 h (Fig. 6B). This external cryogenic trap is akin to the inline trap of the Schlenkputer however the ability to remotely isolate this trap from the reactor by means of the automated side arm is vital to allowing subsequent manipulations without manual intervention. In this case, after automated THF removal the residue was extracted with hexanes and transferred (through a filter-tipped tube) to a collection flask whereby the solvent was removed under reduced pressure to yield pure $Ce(N(SiMe_3)_2)_3$ (compound 2).

Since this cerium complex also exhibits a characteristic yellow colour, indicative of the Ce(III) oxidation state, the product has been characterised by UV-vis spectroscopy. While we have previously demonstrated inline UV/vis analysis, offline sampling may be desirable for some techniques. Thus, a quartz cuvette was designed which allowed facile connection to both the liquid and gas handling systems of our Schlenkputer whilst also being sealable for transport to the relevant spectrometer (Fig. 6c). UV/Vis analysis of the yellow solution was in keeping with published spectra.[25] Subsequent exposure of the sample to air for a brief period (ca. 3 secs) resulted in immediate darkening of the solution to deep orange/brown (See Fig. S12) demonstrating this compounds high reactivity towards air. NMR sampling was also developed and explored for both $CeOTf_3$ and $CeN"_3$. In each case a capillary of deuterated solvent was placed in the NMR tube before it was appended to the Schlenkputer followed by semi-automated transfer of the analyte solution (semi-automated since J Young® tap NMR tubes themselves have not been automated herein). Analytically sampled NMR spectra were in keeping with those collected within an inert atmosphere glovebox.

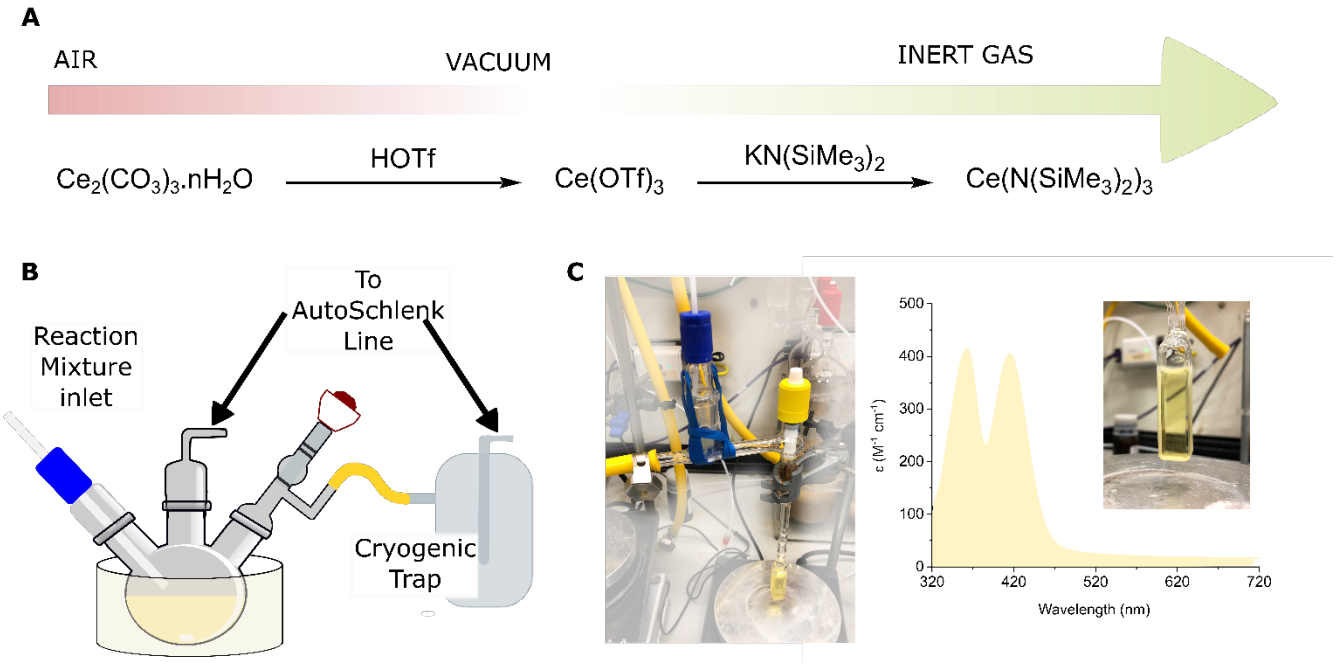


Fig. 6 Synthesis of cerium(III)tris(bis(trimethylsilyl)amine) (2) in two stages. **(A)** Moving from an aerobic to anaerobic and anhydrous synthetic space in the Schlenkputer. **(B)** Setup for removal of solvent using an isolable cryogenic trap. **c**, Automated UV/vis solution sampling allowed for the spectroscopic analysis of the Ce(III) product.

p-block compound - tris(pentafluorophenyl)borane. Tris(pentafluorophenyl)borane (BCF) is a highly moisture sensitive Lewis acid.[28] Acessed through the formation of an aryllithium intermediate, BCF, like many organometallics or other highly-reactive species, is commonly synthesised at very low temperatures (<−70 °C). In addition the final product is often purified by double sublimation or sublimation followed by crystallisation to separate the organic product from LiCl and other impurities, a process which has not previously been automated. This borane also has several valuable NMR handles which can be used to accurately determine the degree of water coordination should the system be exposed to moisture due to dramatically different resonance shifts in the 3- and 4-coordinate examples (Fig. 7A). In order to achieve this synthesis in an automated fashion we therefore required the incorporation of an automated chilling system which was able to reach temperatures as low as −90 °C, a sublimation protocol

for purification of the product under inert conditions and we elected to include inline NMR analysis to provide rapid feedback on the formation of the anhydrous product. Two key reagents for this procedure, n-BuLi and BCl_3 were purchased as solutions and connected directly to the nitrogen and liquid handling systems using needles to minimise the requirement for bespoke equipment. Lithiation and coupling were carried out in a single flask which was cooled to −80 °C automatically (Fig. 7B) before the temperature was autonomously raised to ambient over a period of 120 mins. A portion of the reaction mixture was then transferred to the flow NMR cell appended to the Schlenkputer and subject to ^{19}F NMR which demonstrated formation of the desired product,[29] distinct from the unwanted aquo adduct (−135, −155, −163 ppm) which was not observed (Fig. 7C).[30,31]

Pure, colourless tris(pentafluorophenyl)borane is most commonly obtained through inert-atmosphere sublimation to separate the product from LiCl and other impurities.[32] For manual sublimation it is common to charge a sublimation tube with a solid crude product which can then be heated under vacuum and condenses on either a second room temperature tube or on a cold finger. In order to eliminate this manual step we transfered the product solution into a flask and removed the solvent *in situ*. The reaction mixture was thus transferred into a 3-necked RBF appended with an external cryogenic trap for automated solvent removal (Fig. 7 D/E). As for CeN"$_3$ above, this strategy meant that the solvent could be removed and then isolated in the trap allowing a vacuum pressure sufficient for sublimation to be achieved within the RBF.

s-block complex – Mg(I) dimer. Accessing usual or relatively unstable oxidation states is one common theme in modern organometallic and inert-atmosphere chemistry and is often achieved by exploiting the

reducing power of alkali metals.[33,34,35] However, their use in organic solvents can present hazards which makes their automation challenging and a high level of expertise required for their manual handling.

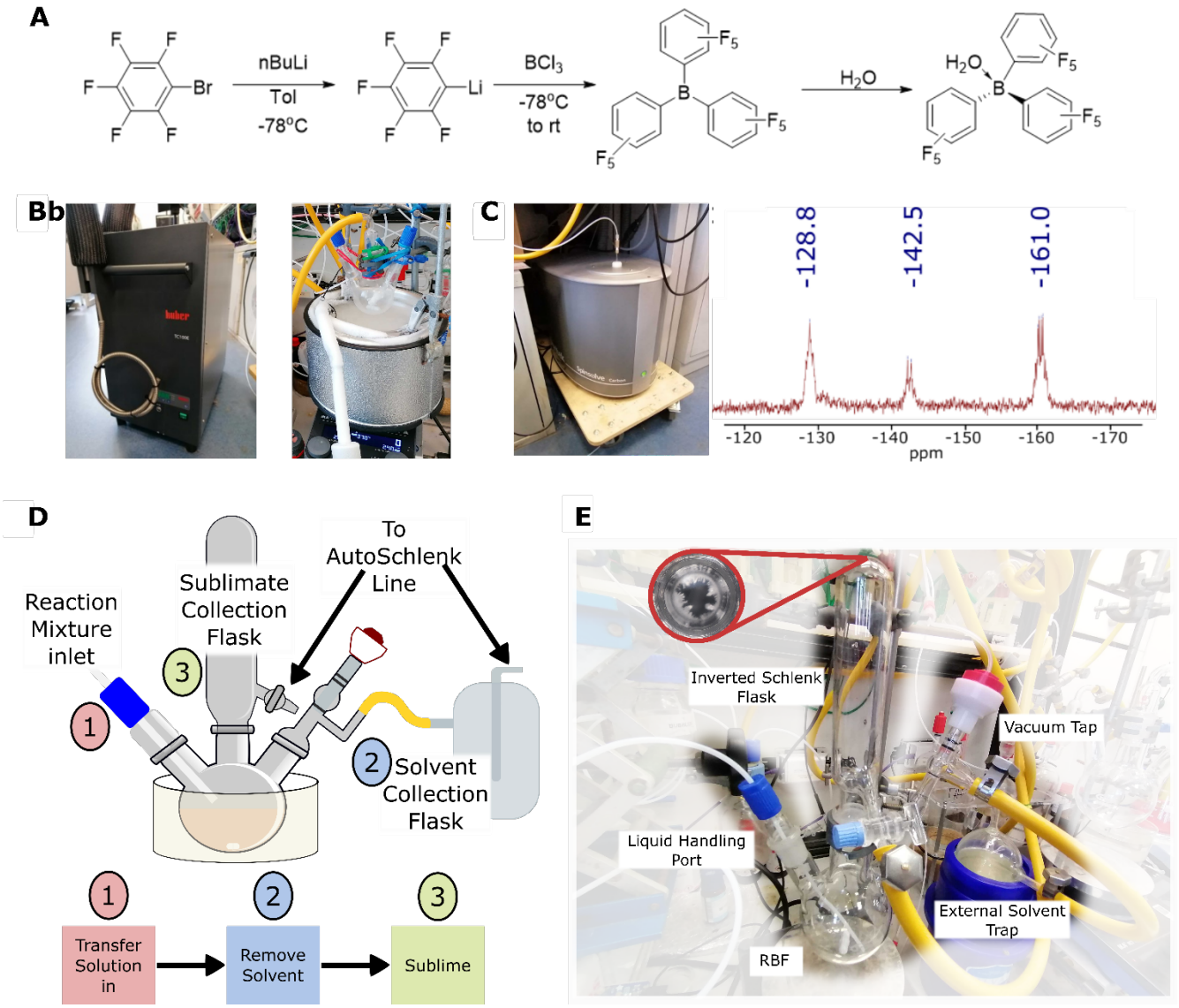


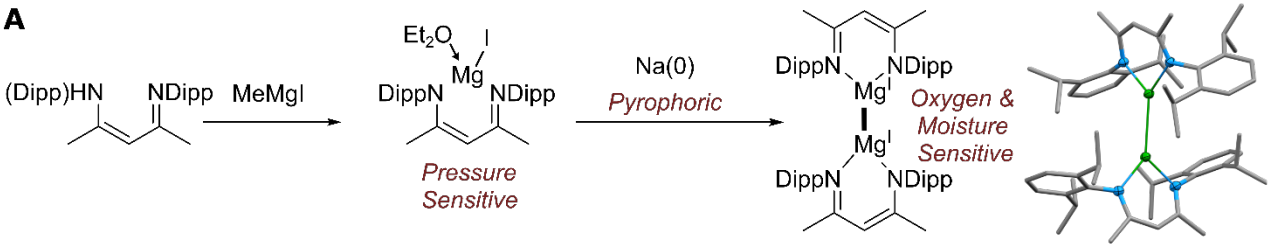
Fig. 7 Synthesis & Isolation of tris(pentafluorophenyl)borane, a highly hygroscopic Lewis acid. (A) Reaction scheme for the synthesis of $B(C_6F_5)_3$. **(B)** Incorporation of an ultra-low temperature chiller unit allowed for automated reactivity at temperatures as low as –100 °C. (**C**) Inline low-field NMR analysis can detect formation of the desired product with no evidence of hydration. **(D)** schematic showing the setup and function of the automated evaporation & sublimation apparatus. **(E)** photograph of the setup and glassware used for automated sublimation of $B(C_6F_5)_3$.

We sought to undertake an alkali metal reduction reaction to yield Stasch & Jones' Mg(I) dimer[36] utilising our Schlenkputer system (Fig. 8A) providing a safe method for reacting with, and quenching Na(0) in automation. Herein we demonstrate mitigation of this risk by use of a temperature probe for real-time feedback upon automated quenching of the alkali metal. For our purposes we can consider the synthesis of Mg(I) as consisting of sets of operations running alongside each other: the Mg(II) reduction and the Na(0) handling. The first step in the magnesium reduction requires the metalation of the ^{Dipp}NacNac ligand (L) to yield moisture and vacuum sensitive $LMgI(OEt_2)_n$ (Fig. 8A). limit the temperature to 50 °C total such that a runaway reaction with evaporation of solvent does not occur.

As for other solid reagents, during setup an RBF was manually charged with the solid ligand (L) while another was similarly charged with a dispersion of Na(0) in oil before cycling of the entire system. This commercially available dispersion exhibits significantly lower sensitivity to air and moisture with the oil acting as a barrier such that handling by non-experts in Schlenk technique can be conducted safely. Automated washing of the sodium metal using hexane removed the oil and provides the highly reactive metal in situ with the filtrate transferred to the waste flask which was maintained under a stream of N_2 for safety (Fig. 8B). Automated addition of MeMgI in toluene (3 M) to the ligand flask at −30 °C yielded a pale yellow solution. Due to the small volume of MeMgI solution added (680 μL) the liquid handling tubing (between valve and reactor) was flushed with additional toluene solvent (7 mL) to ensure stoichiometric reaction. The toluene solution of $LMgI(OEt_2)_n$ was transferred onto a suspension of Na(0) in toluene and the mixture stirred overnight. The solution was then automatically filtered and extracted into hexane to yield the product dimer $[(^{Dipp}NacNac)Mg]_2$, which was confirmed by NMR and XRD analysis.

Before the automated reaction run was completed however, the pyrophoric sodium metal was quenched while maintaining the solution temperature below 50 °C to reduce risk. In order to determine the safest addition rate, we carried out the Na quenching at various aliquot addition volumes and monitored the resulting solution temperature (Fig. 8C). In our work aliquot volume is a proxy for addition rate since an aliquot is added between each temperature measurement. Our analysis found that an aliquot volume of 0.5 mL produced a rather sharp increase in temperature whereas 0.25 mL was deemed to be more appropriate. Importantly, the key XDL command used in this procedure "`AddDynamic`" incorporates feedback to limit the temperature to 50 °C total such that a runaway reaction with evaporation of solvent does not occur.

A



B

PROCESS	RISK	MITIGATION
Wash/Activate Na(0) dispersion in Oil	Na(0) travels through system and is exposed to air	Filter Tip on LH tubing. Waste kept under inert gas
React Na(0) in Toluene	Error occurs when lab is unsupervised	Confirm steps allow supervised automation
Quench Na(0)	Quenching causes exotherm	Temperature Probe limits quenching rate.

C

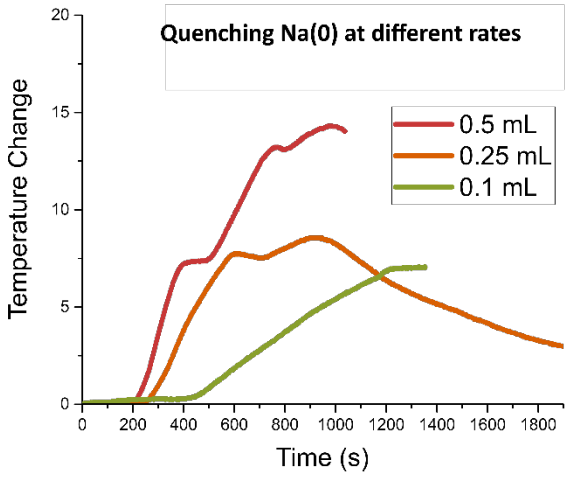


Fig. 8 Alkali metal reduction to generate Mg(I). **(A)** Reduction of (NacNac)MgI with Na(0). **(B)** Risk mitigation steps for automated handling of pyrophoric and flammable species. **(C)** Temperature change with different rates of quenching (rate determined by aliquot size) of Na(0) with *i*PrOH (15% in Toluene). Monitoring stopped upon observation of no further temperature increase.

The automation of the most highly sensitive inert atmosphere synthesis has been demonstrated for the first time. We have described how to design an automatable and remotely operable gas/vacuum handling manifold, Schlenkputer, which can reduce system oxygen and water levels below 1 ppm and demonstrate how to integrate this with a liquid handling robotic platform (Chemputer) to create the Schlenkputer. We have designed a basic set of glassware which can be utilised alongside classical Quickfit® glassware for the undertaking of highly reactive synthesis. In demonstration of the abilities of our system we have synthesised four highly sensitive exemplar compounds from across the periodic table, $Cp_2Ti^{III}(MeCN)_2$ [1], $Ce^{III}\{N(SiMe_3)_2\}_3$ [2], $B(C_6F_5)_3$ [3] and $\{^{Dipp}NacNacMg^{I}\}_2$ [4], each with different synthetic challenges and sensitivity profiles. In this manner we have demonstrated inert atmosphere synthesis, crystallisation, solvent distillation/evaporation and sublimation; as well as analytical sampling, inline analysis, low temperature reactivity, and handling of pyrophoric alkali metals. In all this work demonstrates a comprehensive system for automation of inert atmosphere manipulations, potentially dramatically increasing the safety and throughput of handling highly reactive chemical species.

Resource Availability

The lead contact for this work is Prof. Leroy Cronin. The Supplementary Information file attached includes all materials required to reproduce this work. This includes a .xdl and a .json file for each synthesis and full analytical data as well as details on and photographs of the bespoke hardware described herein to allow reproduction. The software and the code to run the synthesis is attached as a .zip file and will be made available on GitHub upon publication. Supplementary movies show examples of the procedures underway in the Schlenkputer system.

Acknowledgements

The authors would like to sincerely thank Dr Joy Farnaby and her student Tajrian Chowdhury for access to their Glovebox facilities and for sharing of anhydrous $CeOTf_3$ prepared manually by them in their lab. We would also like to thank Daniel Gahler for implementing the remote notification system. We gratefully acknowledge financial support from the EPSRC (Grant Nos. EP/L023652/1, EP/R020914/1, EP/S030603/1, EP/R01308X/1, EP/S017046/1, and EP/S019472/1), the ERC (Project No. 670467 SMART-POM), the EC (Project No. 766975 MADONNA), and DARPA (Project Nos. W911NF-18- 2-0036, W911NF-17-1-0316, and HR001119S0003).

Author Contributions:

The concept was conceived by LC who also managed the team, raised the funding, and designed the programming language. NLB and LC designed the programable manifold, and NLB devised the experiments. Lab work and data analysis was carried out by NLB, FB, AB and DRW. Integration of the low temperature chiller was achieved by VSL. The manuscript and associated materials were prepared by NLB with help from LC.

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Supplementary Information for:

Autonomous Execution of Highly Reactive Chemical Transformations in the Schlenkputer

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1 Chemistry

1.1 General Experimental

All reactions were carried out under inert atmosphere using the technology described herein to evacuate and refill glassware with N_2 gas cylinder purging throughout the reaction. Unless otherwise stated isolated sensitive materials were stored and prepared for offline NMR & XRD analysis in a nitrogen atmosphere MBraun Labstar Glovebox with O_2 levels < 1ppm and H_2O levels <2 ppm. Solvents (excepting hexane) were obtained from an SPS system and dried over activated 3Å molecular sieves for 48h after collection. Anhydrous hexane solvent was purchased from Sigma Aldrich and stored over activated 3Å molecular sieves under nitrogen. Deuterated solvents for NMR analysis were dried over activated 3Å molecular sieves. $NacNac^{Dipp}$ ligand was prepared manually by a published method.[1] Anhydrous Cerium Triflate for the synthesis of $Ce(N\{SiMe_3\}_2)_3$ was kindly provided by Tajrian Chowdhury from the group of Dr Joy Farnaby and prepared manually by their method, prior to our automated synthesis of $CeOTf_3$ described below. Unless otherwise stated all other reagents were purchased from Sigma, Acros, Alfa Aesar, Fisher or Fluorochem and used as received. Inline NMR spectra were collected on Spinsolve 43 Carbon from Magritek at a frequency of 43 MHz while full offline spectra were collected on a on a Bruker Avance III HD 600 MHz or Bruker Avance II 400 MHz spectrometers. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane and for offline samples are referenced to residual protium in the NMR solvent (C_6D_6, δ = 7.16; THF-d_8, δ = 3.58). X-ray crystal structures of compounds **1** & **4** were collected on a Bruker Apex-II diffractometer and confirmed to match CCDC 1167669 (**1**) and CCDC 661566 (**4**) in the CSD. Chilling was provided by a Huber TC100E cooling system.

1.2 **Synthesis of $[Cp_2Ti(CH_3CN)_2]_2[ZnCl_4]$ (1)**

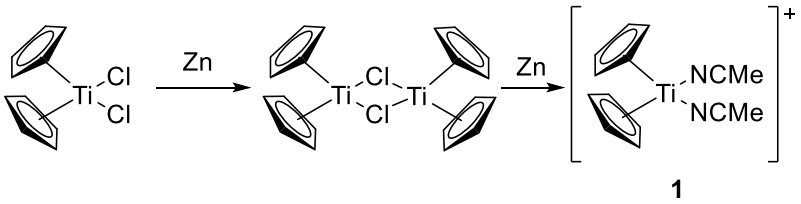


Figure S1: Reaction scheme showing synthesis of compound **1**.

The following procedure was carried out without the use of an inert atmosphere glovebox at any point.

Following an adapted literature procedure,[2] 8.3 g (29.7 mmol, 1 eq.) of Cp_2TiCl_2 was suspended in a mixture of 75 mL THF and 35 mL MeCN under nitrogen. The red solution was then rapidly added to a flask containing Zn dust (2.3 g, 35.2 mmol) and the resulting suspension was stirred for 30 minutes. During this time, the initial red solution turned dark blue. The filtered solution was transferred to a filter flask, and the solution layered with diethyl ether (170 mL). The flask was sealed and allowed to stand for 48h leading to the precipitation of compound **1** as dark blue crystals (5 g, >43 %). In order to extract crystals for X-ray diffraction, Fomblin Y Oil was added to the flask to allow their handling in air. Screening experiments determined the unit cell parameters to be a = 28.4, b = 15.2, c = 15.4 for an Orthorhombic cell with V = 6,648 Å^3 matching CSD entry 1167669.[2] Crystal Data for Compound **1**: *a* = 28.4 Å, *b* = 15.2 Å, *c* = 15.4 Å, $\alpha = \beta = \gamma = 90°$, orthorhombic, *Pbca*.

1.2.1 Hardware Graph

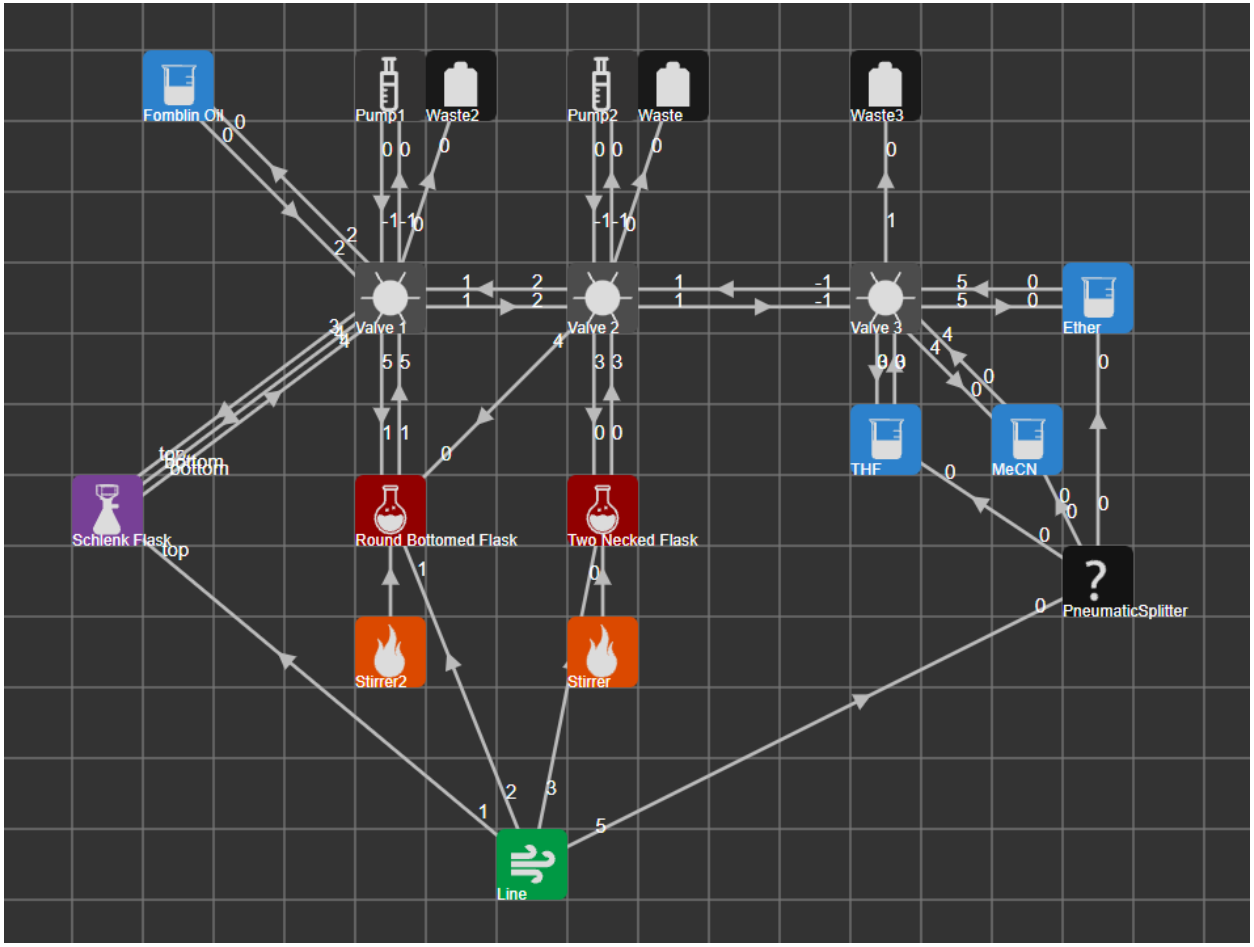


Figure S2: Visual Representation of the hardware graph for the synthesis of $[Cp_2Ti(CH_3CN)_2]_2[ZnCl_4]$ **1**. Full graph file as .json available on https://github.com/croningp and visualisable through https://croningroup.gitlab.io/chemputer/xdlapp/.

1.2.2 Schlenkputer Hardware Setup

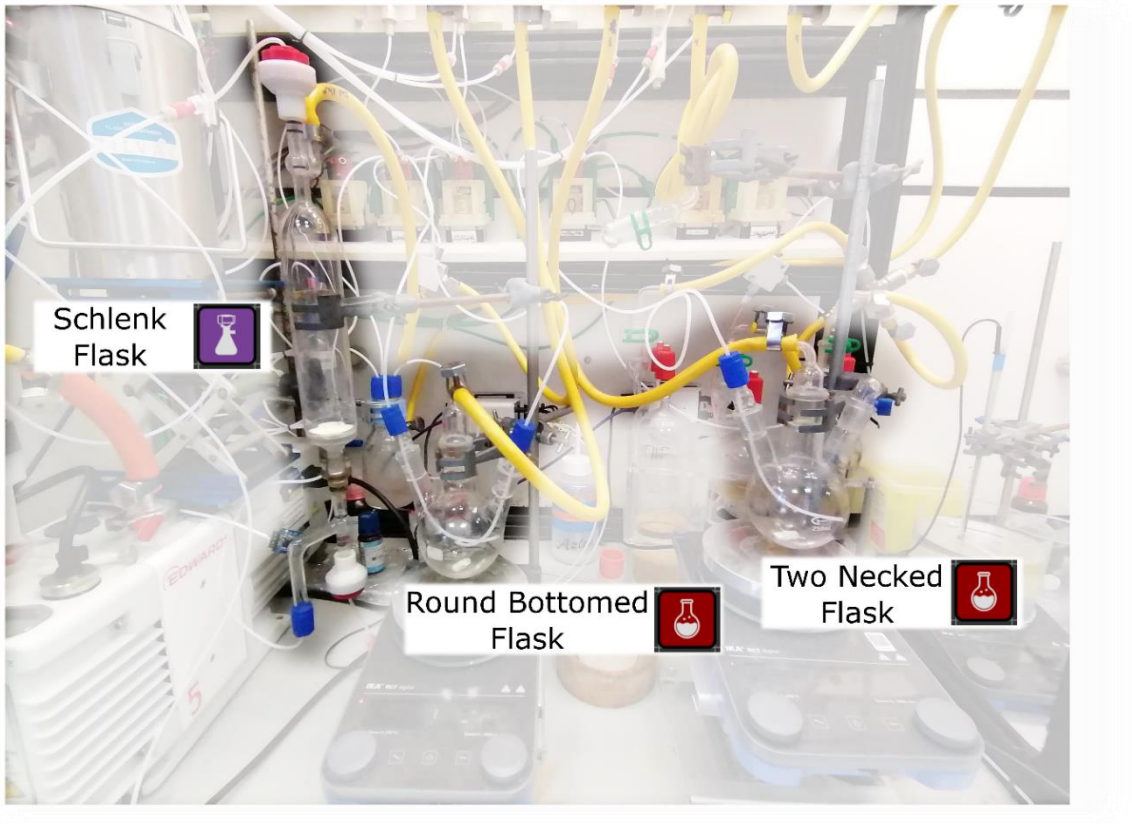


Figure S3: Photograph showing how glassware maps onto Hardware Graph above.

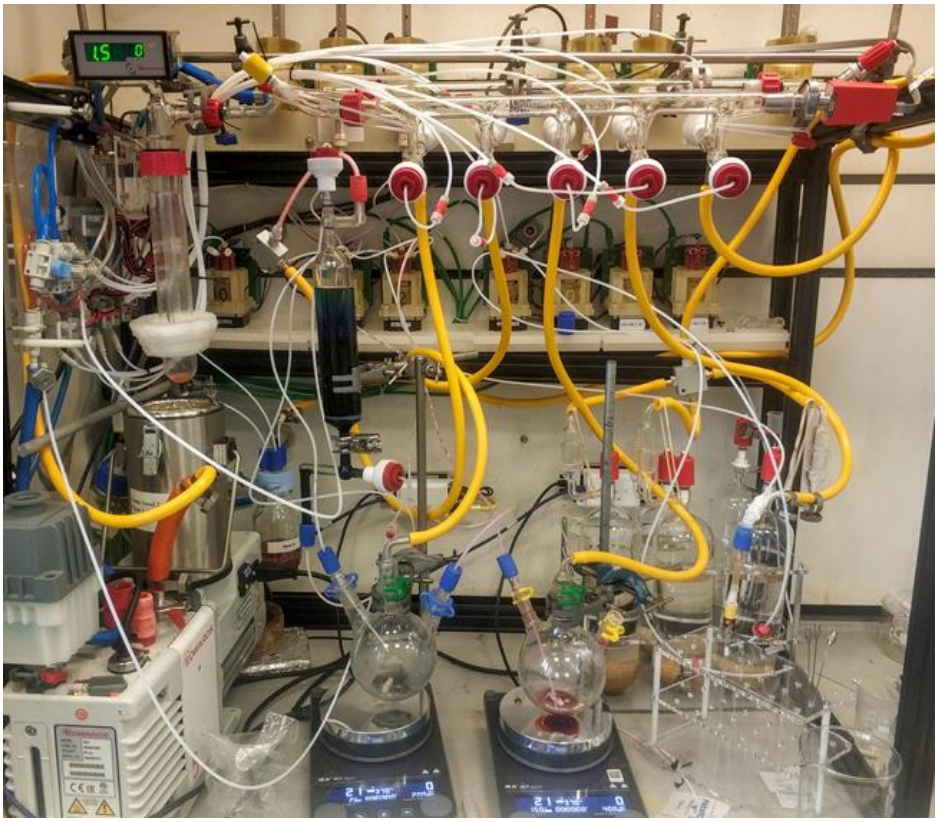


Figure S4: Photograph of synthesis platform during crystallisation.

1.2.3 XDL

The following is the XDL file executed by the platform in concert with the graph shown above (**Figure S2**). The XDL file has three sections: Hardware, Reagents and Procedure. Comments are added in black for clarity of the reader.

```
<Synthesis>

  <Hardware>
      <Component
      id="Pump1"
      type='Pump'
    />
    <Component
      id="Pump2"
      type='Pump'
    />
    <Component
      id="Line"
      type="pneumatic_controller"
    />
    <Component
      id="Waste"
      type='waste'
    />
    <Component
      id="PneumaticSplitter"
      type="custom"
    />
    <Component
      id="Schlenk Flask"
      type="filter"
    />
    <Component
      id="Round Bottomed Flask"
      type="reactor"
    />
     <Component
      id="Two Necked Flask"
      type="reactor"
    />
    <Component
      id="Valve 1"
      type='Valve'
    />
    <Component
      id="Valve 2"
      type='Valve'
    />
  </Hardware>

  <Reagents>
   <Reagent
        name='Cp2TiCl2'
        type='solvent'
    />
    <Reagent
        name='Zinc Dust'
        type='solvent'
    />
    <Reagent
        name='MeCN'
        type='solvent'
    />
    <Reagent
        name='THF'
```

```
        type='solvent'
    />
    <Reagent
        name='Ether'
        type='solvent'
    />
    <Reagent
        name="Oil"
        type='solvent'
    />
</Reagents>



<Procedure>

    <!-- Connecting Schlenk Flask hot out of the oven and pulling vaccum -->

    <Confirm
        msg = 'Is Schlenk Flask Connected?'
    />
    <SchlenkFlaskTapOpen
        pneumatic_controller='Line'
        position='top'
    />
    <CConnect
        from_vessel = 'Schlenk Flask'
        to_vessel = 'Pump1'
    /> <!--CConnect allows us to vac out the tubing up to the pump-->
    <SchlenkLineTapOpenVacuum
        pneumatic_controller='Line'
        port='1'
    />

    <!-- Connecting Round Bottomed Flask Flask hot out of the oven and pulling vaccum -->

    <Confirm
        msg = 'Is Round Bottomed Flask Connected?'
    />
    <CConnect
        from_vessel = 'Round Bottomed Flask'
        to_vessel = 'Pump1'
    />
    <SchlenkLineTapOpenVacuum
        pneumatic_controller='Line'
        port='2'
    />

    <!-- Connecting Two Necked Flask Flask hot out of the oven and pulling vaccum -->

    <Confirm
        msg = 'Is Two Necked Flask Connected?'
    />
    <CConnect
        from_vessel = 'Two Necked Flask'
        to_vessel = 'Pump2'
    />
    <SchlenkLineTapOpenVacuum
        pneumatic_controller='Line'
        port='3'
    />

    <Wait
        time = '5 minutes'
    /> <!-- Lets the flasks cool to room temp.-->

    <!-- Starting to purge Two Necked Flask with  N2, manually charging it with Cp2TiCl2,
         then pulling vacuum -->

    <StartPurge
        vessel = 'Two Necked Flask'
    />
    <AddSolid
```

```
        vessel = 'Two Necked Flask'
        reagent = 'Cp2TiCl2'
        mass = '8.3 g'
        confirm_solid = 'True'
    />
    <SchlenkLineTapOpenVacuum
        pneumatic_controller='Line'
        port='3'
    />

    <!-- Starting to purge Round Bottomed Flask and manually charging it with Zinc metal dust,
         then pulling vacuum -->

    <StartPurge
        vessel = 'Round Bottomed Flask'
    />
    <AddSolid
        vessel = 'Round Bottomed Flask'
        reagent = 'Zinc Dust'
        mass = '2.3 g'
        confirm_solid = 'True'
    />

    <SchlenkLineTapOpenVacuum
        pneumatic_controller='Line'
        port='2'
    />

    <!—
- Alternately pulling vacuum and purging on the three flasks, three times. The Async command allows all of th
ese flasks to be evacuated and refilled at the same time-->

    <Async><!-- this splits the gas line to connect to all three solvent flasks -->
        <EvacuateAndRefill
            vessel='PneumaticSplitter'
            after_vacuum_wait_time='3 minutes'
            repeats='3'
            gas='low'
        />
    </Async>
    <Async>
        <EvacuateAndRefill
            vessel='Two Necked Flask'
            after_vacuum_wait_time='3 minutes'
            repeats='3'
            gas='low'
        />
    </Async>
    <Async>
        <Wait
            time = '5 seconds'
        />
        <EvacuateAndRefill
            vessel='Round Bottomed Flask'
            after_vacuum_wait_time='3 minutes'
            repeats='3'
            gas='high'
        />
    </Async>
    <Async>
        <Wait
            time = '10 seconds'
        />
        <EvacuateAndRefill
            vessel='Schlenk Flask'
            after_vacuum_wait_time='3 minutes'
            repeats='3'
            gas='high'
        />
    </Async>
    <Wait
        time = '13 mins'
    />
```

```
<!—Putting all three flasks under N2 to begin the reaction -->

<StartPurge
    vessel = 'Schlenk Flask'
/>
<StartPurge
    vessel = 'Round Bottomed Flask'
/>
 <StartPurge
    vessel = 'Two Necked Flask'
/>
<!—-Putting the solvents under N2 and manually connecting tubing to solvent -->

<StartPurge
    vessel = 'PneumaticSplitter'
/>
<Confirm
    msg = 'Are the three solvents connected?'
/>

<!-- Priming and clearing the backbone of air before solvent addition-->

<ResetHandling
    solvent='THF'
    repeats='3'
    volume='5mL'
/>

<!-- Step 1: Add Solvents & Stir-->
<Add
    reagent='THF'
    vessel='Two Necked Flask'
    volume = '75 mL'
/>
<ResetHandling
    solvent='MeCN'
    repeats='3'
    volume='5mL'
/>
<Add
    reagent='MeCN'
    vessel='Two Necked Flask'
    volume = '25 mL'
/>
<Stir
    vessel='Two Necked Flask'
    time= '40 mins'
    stir_speed = '200'
/>

<!-- Add solution of Cp2TiCl2 to Flask containing Zn Dust-->

<StartStir
    vessel='Round Bottomed Flask'
    stir_speed = '200'
/>
<Transfer
    from_vessel='Two Necked Flask'
    to_vessel='Round Bottomed Flask'
    volume = '100 mL'
    rinsing_solvent = 'MeCN'
    rinsing_volume = '5 mL'
    rinsing_repeats = '2'
    aspiration_speed = '100'
    move_speed = '50'
    dispense_speed = '200'
/>
<StopStir
    vessel = 'Two Necked Flask'
/>

<!-- Reduction through Zn metal dust takes place over 30 minutes, while solution changes colour -->

<Wait
```

```
        time = '30 mins'
    />

    <!-- Opening bottom tap of Schlenk Flask and addition of Diethyl Ether from the bottom -->
    <SchlenkFlaskTapOpen
        pneumatic_controller='Line'
        position='bottom'
    />
    <AddFilterDeadVolume
        filter_vessel = 'Schlenk Flask'
        solvent = 'Ether'
        volume = '20 mL'
    />
    <SchlenkFlaskTapClose
        pneumatic_controller='Line'
        position='bottom'
    />

    <!--Transfering reaction mixture from Round Bottomed Flask through filter into Schlenk Flask-->
    <SchlenkFlaskTapOpen
        pneumatic_controller='Line'
        position='top'
    />
    <Transfer
        from_vessel='Round Bottomed Flask'
        to_vessel='Schlenk Flask'
        to_port='top'
        volume = '130 mL'
    />
    <!-- Layering of diethyl ether ontop of solution and waiting 48h for crystallisation to occur  -->
    <Add
        reagent='Ether'
        vessel='Schlenk Flask'
        volume = '150 mL'
    />
    <Wait
        time = '72 h'
    />

    <!-
- Removing liquid from the bottom of Schlenk Flask with filter, leaving solid product in Schlenk Flask-->

    <SchlenkFlaskTapOpen
        pneumatic_controller='Line'
        position='bottom'
    />
    <Transfer
        from_vessel='Schlenk Flask'
        from_port='bottom'
        to_vessel='Waste'
        volume = '350 mL'
    />
    <SchlenkFlaskTapClose
        pneumatic_controller='Line'
        position='bottom'
    />

    <!-- Addition of Oil prepares and protects obtained blue crystals for x-ray crystallography,
         closing of taps at Schlenk Flask stores product under nitrogen,
         to transport it conveniently to x-ray machine -->

    <SchlenkFlaskTapOpen
        pneumatic_controller='Line'
        position='top'
    />
    <Add
        reagent='Oil'
        vessel='Schlenk Flask'
        port='top'
        volume='20 mL'
    />
    <SchlenkFlaskTapClose
        pneumatic_controller='Line'
        position='top'
```

```
    />

  </Procedure>
</Synthesis>
```

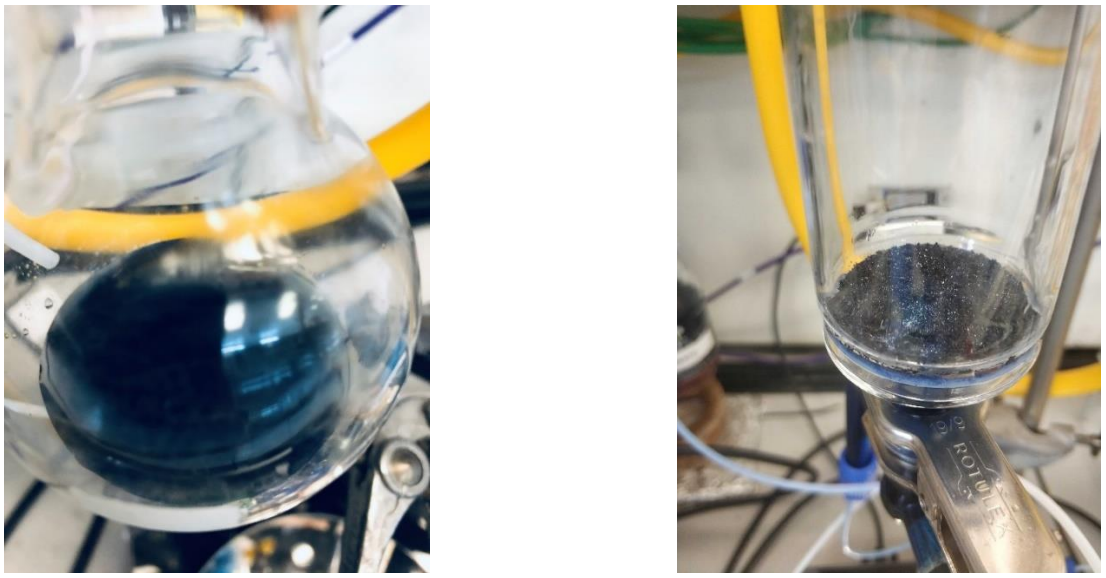


Figure S5: Photographs showing the solution of Ti(III) after filtration (left) and the crystals formed (right).

1.3 Synthesis of $Ce(N(SiMe_3)_2)_3$ (2)

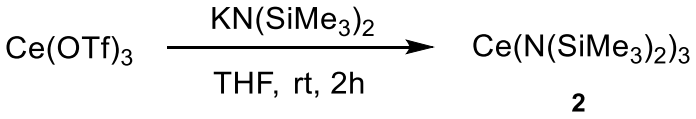


Figure S6: Reaction scheme for the synthesis of CeN''_3 (compound **2**).

Following an adapted literature procedure[3] the white powders $Ce(OTf)_3$ (0.5 g, 0.867 mmol, 1.0 equivalent) and $KN(SiMe_3)_2$ (KN", 540 mg, 2.707 mmol, 3.1 equiv.) were weighed into a J-Youngs tapped ampoule in the glovebox. THF (10 mL) was added to suspend the reagents and a slow colour change from colourless to pale yellow was observed. The mixture was stirred at room temperature for 2 hours before being transferred into a second flask with washing with THF (10 mL). Subsequently, the THF was distilled into a cryogenic trap for 16 h before the orange residue was extracted into hexane (3 x 10 mL) and transferred through a filter tipped tube into a collection flask. The extractions in hexane were pumped down yielding a yellow powder CeN''_3 (187 mg, 35%).

Analytical data was consistent with literature reported values for $[Ce(N(SiMe_3)_2)_3)]$.[3,4]

^{1}H NMR (C_6D_6): δ −3.36 (54H, s, $Ce(N(SiMe_3)_2)_3$) ppm. A small amount of HN" impurity (δ 0.10, ~3.8%) was also present.

1.3.1 Hardware Graph

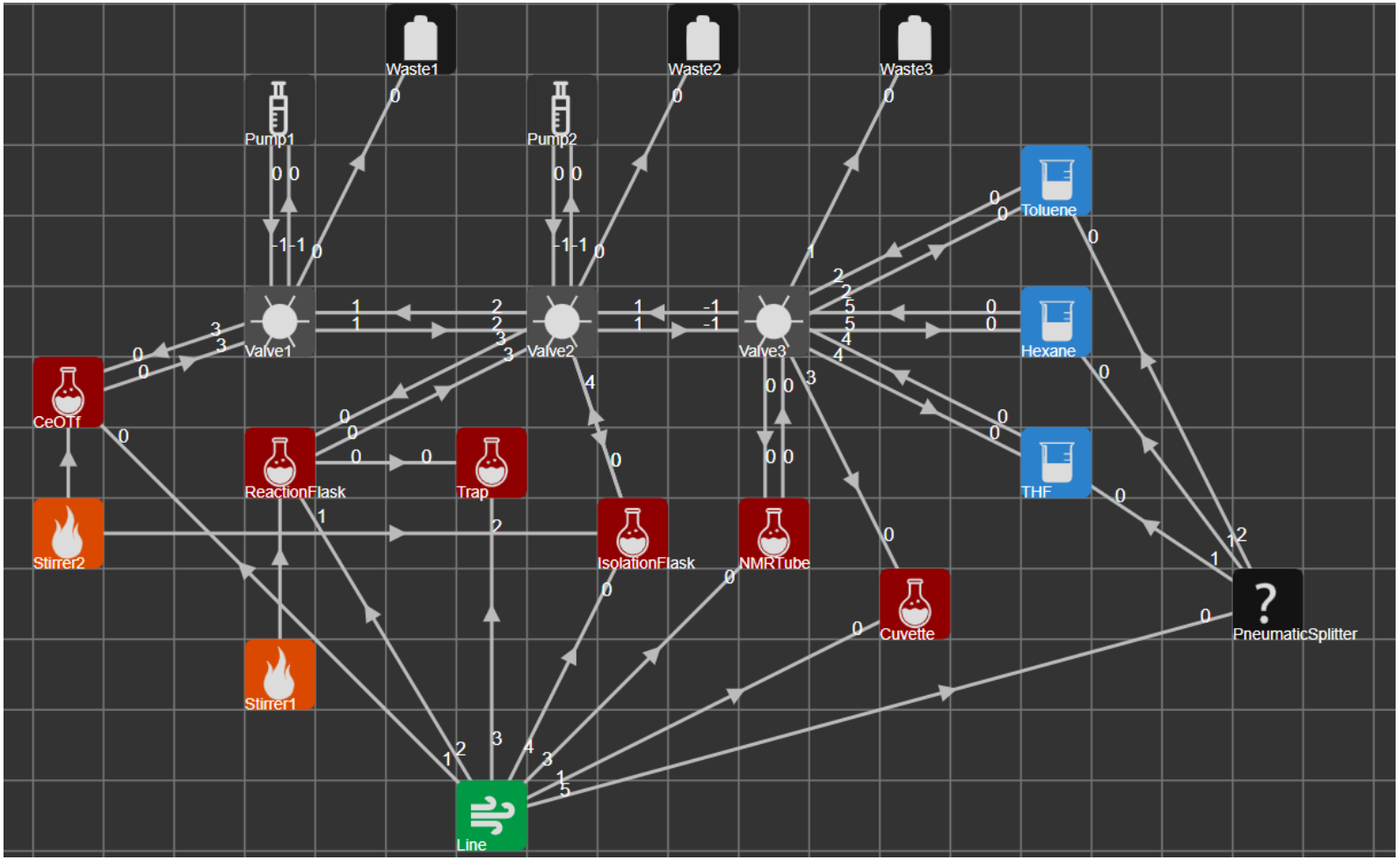


Figure S7: Visual Representation of the hardware graph for the synthesis of CeN"$_3$. Full graph file as .json available on https://github.com/croningp and visualisable through https://croningroup.gitlab.io/chemputer/xdlapp/.

1.3.2 XDL – $Ce\{N(SiMe_3)_2\}_3$ synthesis

The following is the XDL file executed by the platform in concert with the graph shown above (**Figure S7**). The XDL file has three sections: Hardware, Reagents and Procedure. Comments are added in black for clarity of the reader.

```
<Synthesis>
    <Hardware>
        <Component
        id="PneumaticSplitter"
        type="custom"
        />
        <Component
        id="Trap"
        type="reactor"
        />
        <Component
        id="ReactionFlask"
        type="reactor"
        />
        <Component
        id="IsolationFlask"
        type="reactor"
        />
        <Component
        id="CeOTf"
        type="reactor"
        />
        <Component
        id="Cuvette"
        type="reactor"
        />
        <Component
        id="NMRTube"
        type="reactor"
        />
        <Component
        id="Line"
        type="pneumatic_controller"
        />
        <Component
        id="Valve1"
        type='Valve'
        />
        <Component
        id="Valve2"
        type='Valve'
        />
        <Component
        id="Valve3"
        type='Valve'
        />
        <Component
        id="Pump1"
        type='Pump'
        />
        <Component
        id="Pump2"
        type='Pump'
        />
        <Component
        id="Waste3"
        type='Waste'
        />
        <Component
        id="Waste1"
        type='Waste'
        />
        <Component
```

```
        id="Waste2"
        type='Waste'
        />
    </Hardware>

    <Reagents>
        <Reagent
            name='Toluene'
            type='solvent'
        />
        <Reagent
            name='Hexane'
            type='solvent'
        />
        <Reagent
            name='THF'
            type='reagent'
        />
        <Reagent
            name='CeOTf3'
            type='solid'
        />
        <Reagent
            name='KN'
            type='solid'
        />

    </Reagents>

    <Procedure> -
        <!--Reaction Setup -->
        <!--Connect Reaction Flasks-->
        <Confirm
            msg = 'Is CeOTf Connected?'
        />
        <SchlenkLineTapOpenVacuum
        pneumatic_controller='Line'
        port='1'
        />
        <CConnect
            from_vessel = 'CeOTf'
            to_vessel = 'Pump1'
        />
        <Confirm
            msg = 'Is ReactionFlask Connected?'
        />
        <SchlenkLineTapOpenVacuum
        pneumatic_controller='Line'
        port='2'
        />
        <CConnect
            from_vessel = 'ReactionFlask'
            to_vessel = 'Pump2'
        />
        <Wait
            time = '2 min'
        />
        <Confirm
            msg = 'Are flasks cool to rt?'
        />
        <!-- EvacuateAndRefill Steps for Flasks-->
        <Async>
            <EvacuateAndRefill
                vessel='CeOTf'
                after_vacuum_wait_time='3 minutes'
                after_inert_gas_wait_time = '2 mins'
                repeats='3'
                gas='high'
            />
        </Async>
        <Async>
            <EvacuateAndRefill
                vessel='ReactionFlask'
                after_vacuum_wait_time='3 minutes'
```

```
            after_inert_gas_wait_time = '2 mins'
            repeats='3'
            gas='high'
        />
    </Async>
    <Async>
        <EvacuateAndRefill
            vessel='PneumaticSplitter'
            after_vacuum_wait_time='3 minutes'
            after_inert_gas_wait_time = '2 mins'
            repeats='3'
            gas='high'
        />
    </Async>
    <Wait
        time = '16 mins'
    />
    <Confirm
        msg = 'Are the solvents connected to the liquid handling backbone?'
    />
    <ResetHandling
        solvent='THF'
        repeats='4'
        volume='5mL'
    />
    <!-- Step 1 - Begin Reaction -->
    <Add
        reagent='THF'
        vessel='CeOTf'
        volume = '10 mL'
        stir = 'true'
        stir_speed = '500'
        aspiration_speed = '5'
    />
    <Stir
        vessel = 'CeOTf'
        stir_speed = '500'
        time = '2h'
    />
    <Transfer
        from_vessel='CeOTf'
        to_vessel='ReactionFlask'
        aspiration_speed = '5'
        volume = '20 mL'
        rinsing_solvent = 'THF'
        rinsing_volume = '10 mL'
        rinsing_repeats = '1'
    />

    <!--Step 3 -->
    <Confirm
        msg = 'Is the cryo trap filled with liquid N2?'
    />
    <StartStir
        vessel = 'ReactionFlask'
        stir_speed = '500'
    />
    <SchlenkLineTapClose
        pneumatic_controller = 'Line'
        port = '2'
    />
    <SchlenkLineTapOpenVacuum
        pneumatic_controller = 'Line'
        port = '3'
    />
    <SchlenkFlaskTapOpen
        pneumatic_controller = 'Line'
        position = 'bottom'
    />
    <Wait
        time = '30 mins'
    />
    <SchlenkFlaskTapClose
        pneumatic_controller = 'Line'
```

```
        position = 'bottom'
    />
    <SchlenkLineTapClose
        pneumatic_controller = 'Line'
        port = '3'
    />
    <SchlenkLineTapOpenArgon
        pneumatic_controller = 'Line'
        port = '2'
    />


    <!--Insert Analytical Sampling steps here if required (see below) -->


    <SchlenkLineTapOpenVacuum
        pneumatic_controller = 'Line'
        port = '2'
    />
    <!--Evacuate flask directly overnight -->
    <SchlenkLineTapOpenVacuum
        pneumatic_controller = 'Line'
        port = '2'
    />
    <Wait
        time = '16 h'
    />
    <SchlenkLineTapOpenArgon
        pneumatic_controller = 'Line'
        port = '2'
    />

    <!--Day 2: Setup Isolation Flask and reinertise the system for completeness/robustness-->
    <Confirm
        msg = 'Is IsolationFlask Connected?'
    />
    <SchlenkFlaskTapOpen
        pneumatic_controller = 'Line'
        position = 'top'
    />
    <SchlenkLineTapOpenVacuum
        pneumatic_controller='Line'
        port='4'
    />
    <CConnect
        from_vessel = 'IsolationFlask'
        to_vessel = 'Pump2'
    />
    <Wait
        time = '2 min'
    />
    <Confirm
        msg = 'Is IsolationFlask cool to rt?'
    />
    <SchlenkFlaskTapOpen
        pneumatic_controller = 'Line'
        position = 'top'
    />
    <Async>
        <EvacuateAndRefill
            vessel='PneumaticSplitter'
            after_vacuum_wait_time='3 minutes'
            after_inert_gas_wait_time = '2 mins'
            repeats='3'
            gas='high'
        />
    </Async>
    <Async>
        <EvacuateAndRefill
            vessel='IsolationFlask'
            after_vacuum_wait_time='3 minutes'
            after_inert_gas_wait_time = '2 mins'
            repeats='3'
            gas='high'
```

```
            />
        </Async>
        <Wait
            time = '16 mins'
        />
        <Confirm
            msg = 'Are the solvents connected to the liquid handling backbone?'
        />
        <ResetHandling
            solvent='Hexane'
            repeats='3'
            volume='5mL'
        />


        <!—Step 4: Hexane extraction -->
        <Add
            reagent='Hexane'
            vessel='ReactionFlask'
            volume = '20 mL'
            stir = 'true'
            stir_speed = '300'
        />
        <Stir
            stir_speed = '300'
            vessel='ReactionFlask'
            time = '10 min'
        />
        <Transfer
            from_vessel='ReactionFlask'
            to_vessel='IsolationFlask'
            aspiration_speed = '10'
            volume = '60 mL'
        />
        <StartStir
            stir_speed = '1000'
            vessel='IsolationFlask'
        />
        <Wait
            time = '1 min'
        />
        <SchlenkLineTapOpenVacuum
            pneumatic_controller='Line'
            port = '4'
        />
        <SchlenkFlaskTapClose
            pneumatic_controller = 'Line'
            position = 'top'
        />
    </Procedure>
</Synthesis>
```

1.3.3 XDL – Analytical Sampling

Coloured components of the XDL file below can be added to the above XDL (CeN”$_3$ synthesis) where indicated above (i.e. before Day 2: Isolation steps) for integrated synthesis and analysis. The following XDL was run as a stand alone method for our testing.

```
<Synthesis>
    <Hardware>
        <Component
        id="PneumaticSplitter"
        type="reactor"
        />
        <Component
```

```
        id="ReactionFlask"
        type="reactor"
        />
        <Component
        id="Cuvette"
        type="reactor"
        />
        <Component
        id="NMRTube"
        type="reactor"
        />
        <Component
        id="Line"
        type="pneumatic_controller"
        />
        <Component
        id="Valve1"
        type='Valve'
        />
        <Component
        id="Valve2"
        type='Valve'
        />
        <Component
        id="Valve3"
        type='Valve'
        />
        <Component
        id="Pump1"
        type='Pump'
        />
        <Component
        id="Pump2"
        type='Pump'
        />
        <Component
        id="Waste3"
        type='Waste'
        />
        <Component
        id="Waste1"
        type='Waste'
        />
        <Component
        id="Waste2"
        type='Waste'
        />
    </Hardware>

    <Reagents>
        <Reagent
            name='Toluene'
            type='solvent'
        />
        <Reagent
            name='Hexane'
            type='solvent'
        />
        <Reagent
            name='THF'
            type='reagent'
        />
    </Reagents>

    <Procedure>
    <!--Analytical Sampling Steps-->
        <Confirm
            msg = 'Is Cuvette connected?'
        />
        <!-- Evacuating air from cuvette tubing (path Cuvette-Valve3-Valve2-Pump2) -->
        <CValveMoveToPosition
            valve_name = 'Valve3'
            position = '3'
        />
```

```
        <SchlenkLineTapOpenVacuum
            pneumatic_controller = 'Line'
            port = '1'
        />
        <Confirm
            msg = 'Is JY NMR Tube connected?'
        />
        <SchlenkLineTapOpenVacuum
            pneumatic_controller = 'Line'
            port = '3'
        />
        <Wait
            time = '2 mins'
        />
        <Confirm
            msg = 'Is ReactionFlask connected?'
        />
        <CConnect
            from_vessel = 'ReactionFlask'
            to_vessel = 'Pump2'
        />
        <!-- Evacuate-refill solvent splitter, ReactionFlask and Cuvette -->
        <Async>
            <EvacuateAndRefill
                vessel='PneumaticSplitter'
                after_vacuum_wait_time='2 minutes'
                after_inert_gas_wait_time = '2 mins'
                repeats='3'
                gas='high'
            />
        </Async>
        <Async>
            <EvacuateAndRefill
                vessel = 'ReactionFlask'
                after_vacuum_wait_time='2 minutes'
                after_inert_gas_wait_time = '2 mins'
                repeats='3'
                gas='high'
        />
        </Async>
        <Async>
            <EvacuateAndRefill
                vessel = 'Cuvette'
                after_vacuum_wait_time='2 minutes'
                after_inert_gas_wait_time = '2 mins'
                repeats='3'
                gas='high'
            />
        </Async>
        <Async>
            <EvacuateAndRefill
                vessel = 'NMRTube'
                after_vacuum_wait_time='2 minutes'
                after_inert_gas_wait_time = '2 mins'
                repeats='3'
                gas='high'
            />
        </Async>
        <Wait
            time = '15 mins'
        />
        <Confirm
            msg = 'Are ReactionFlask and Solvents connected to liquid backbone?'
        />
        <ResetHandling
            solvent='Toluene'
            repeats='3'
            volume='5mL'
        />
        <Add
            reagent='Toluene'
            vessel='ReactionFlask'
            volume = '15 mL'
            stir = 'true'
```

```
            stir_speed = '900'
            aspiration_speed = '5'
        />
        <StartStir
            stir_speed = '400'
            vessel='ReactionFlask'
        />
        <Wait
            time = '10 mins'
        />
        <!--Transfer UV/vis/NIR/Luminesence sample to cuvette and seal up-->
        <Transfer
            from_vessel='ReactionFlask'
            to_vessel='Cuvette'
            aspiration_speed = '5'
            volume = '5 mL'
        />
        <SchlenkLineTapOpenVacuum
            pneumatic_controller = 'Line'
            port = '3'
        />
        <!--Transfer NMR sample to J-Youngs tapped NMR tube and seal up-->
        <Confirm
            msg = 'Is NMR tube sealed under vacuum?'
        />
        <Transfer
            from_vessel='ReactionFlask'
            to_vessel='NMRTube'
            aspiration_speed = '5'
            volume = '3 mL'
        />
        <Confirm
            msg = 'Is NMR tube opened to pull through solution?'
        />
        <SchlenkLineTapOpenArgon
            pneumatic_controller = 'Line'
            port = '3'
        />
        <Confirm
            msg = 'Are cuvette, NMR tube and solvents sealed?'
        />
        <SchlenkLineTapClose
            pneumatic_controller='Line'
            port = '1'
        />
        <SchlenkLineTapClose
            pneumatic_controller='Line'
            port = '3'
        />
    </Procedure>
</Synthesis>
```

1.3.4 Analytical Data

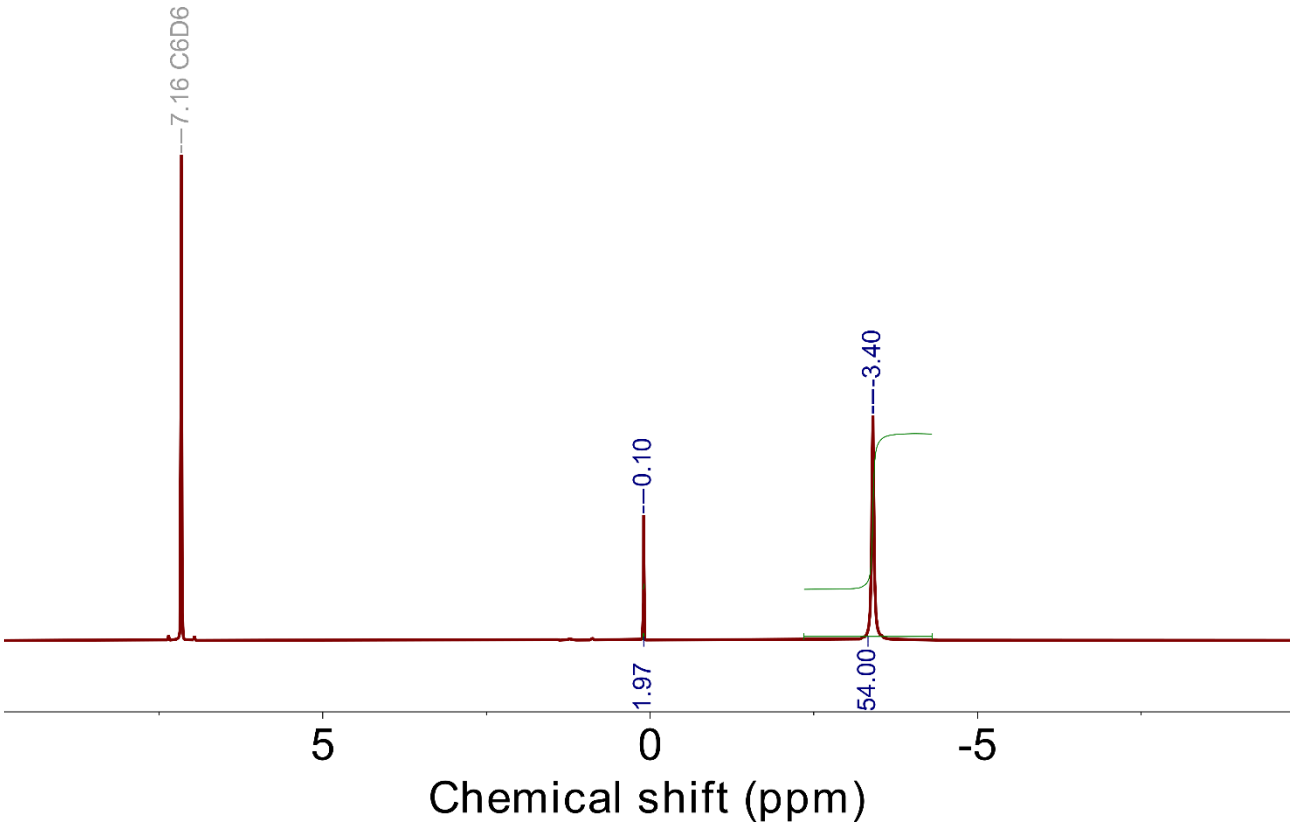


Figure S8: ^{1}H NMR spectrum of CeN"$_3$ (-3.40 ppm). >97% pure by NMR.

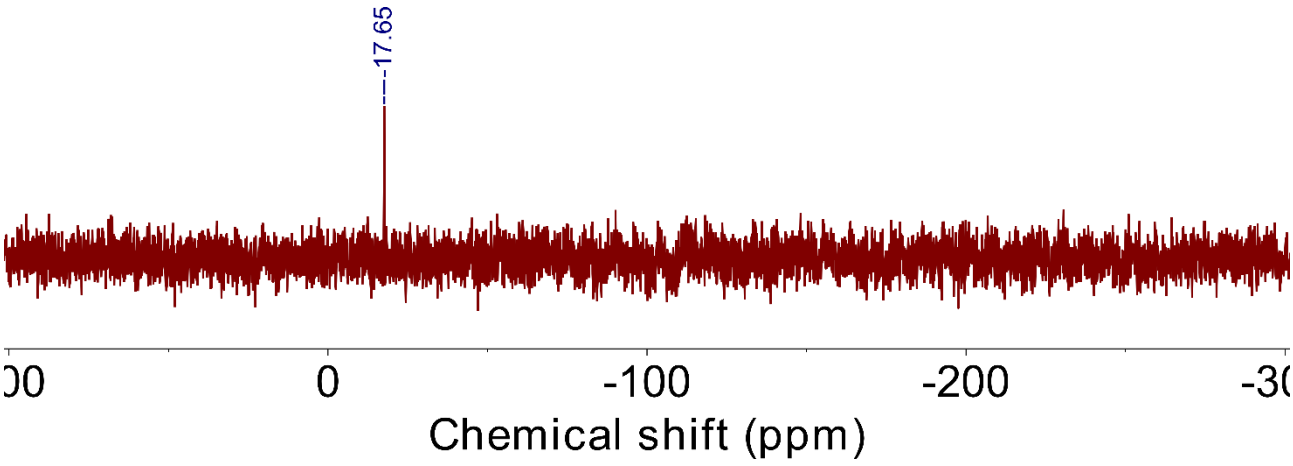


Figure S9: ^{29}Si NMR spectrum of CeN"$_3$.

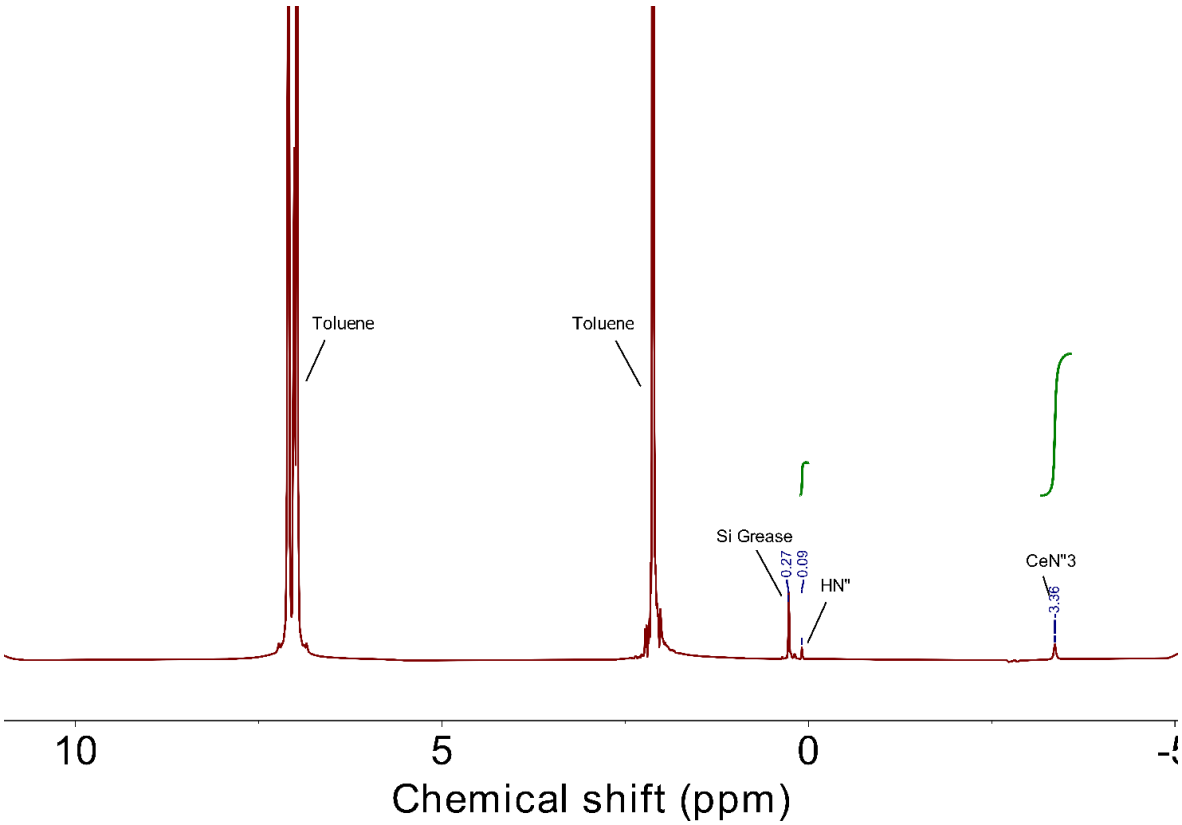


Figure S10: Semi-Automatically sampled ^{1}H NMR spectrum of CeN"$_3$ solution in H_8-toluene (with C_6D_6 capillary in tube for locking).

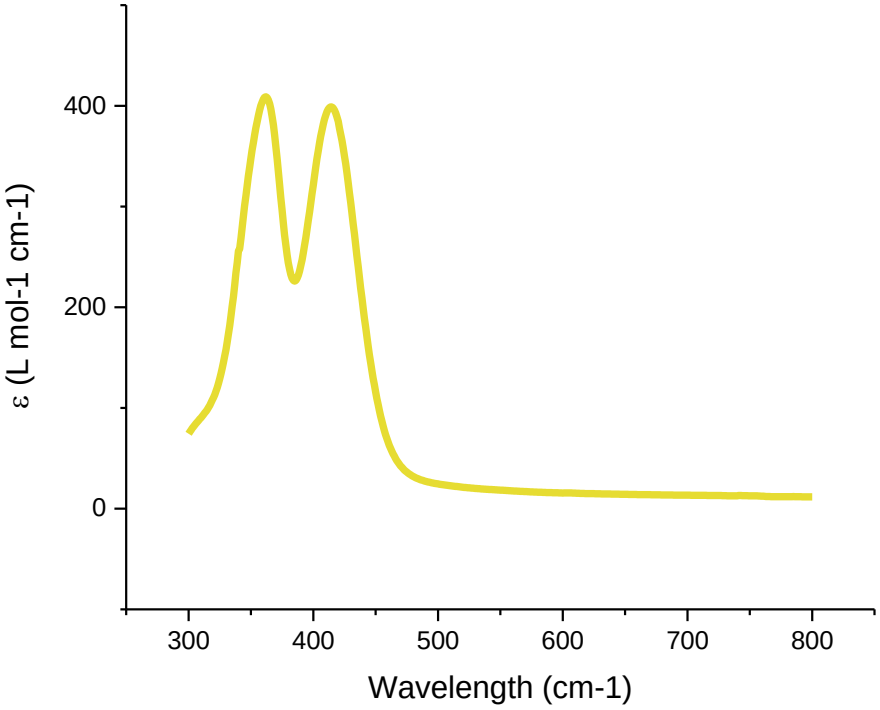


Figure S11: Automatically sampled UV/vis spectrum of CeN"$_3$ in toluene (ca. 4 mM).

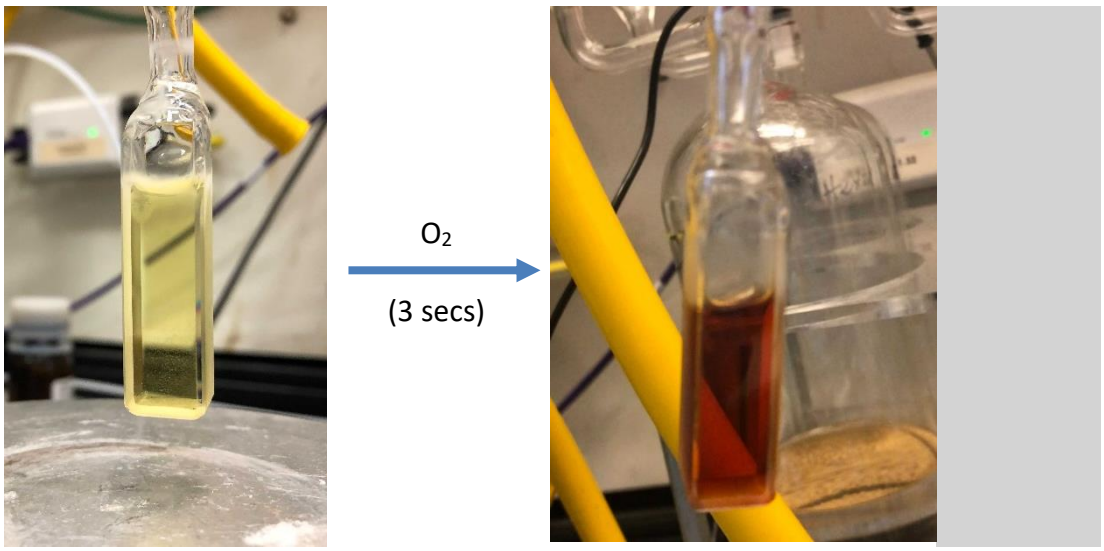


Figure S12: Cerium(III) tris(bis(trimethylsilylamide)) before and after exposure to air for 3s.

1.3.5 Synthesis of $CeOTf_3$ – testing handling of corrosives in system

Following a literature procedure an RBF was charged with $Ce_2(CO_3)_3.xH_2O$ (1.5 g, 3.26 mmol, 1 equiv.) and suspended in 20 mL of deionised water.[5] Neat HOTf (2 mL, 22.6 mmol, 6.9 equiv.) was added to the suspension, with stirring, resulting in an immediate vigorous fuming of the solution. The reaction mixture was refluxed at 101°C for 18 hours under a flow of N_2. After 18 hours all solids had dissolved, leaving a colourless solution. Water was removed and the white solids were washed with Et_2O (4 × 10 mL) and hexanes (2 × 10 mL), and dried at 220°C for 36 hours; yielding a whitish free flowing powder. The complete removal of water was confirmed by the absence of the key -OH band at 1657 cm^{-1} which is present in the hydrated salt (Figure S16) upon rapid IR analysis of the solid material by ATR-IR in air.[5] Semi-automated NMR sampling of the white solids in dry MeCN into a J-Youngs NMR tube containing a capillary of d_3-MeCN (**Figure S13B**) showed only solvent in the ^1H spectrum (**Figure S17**) and a single ^{19}F resonance at −74.1 ppm (**Figure S16**, $CeOTf_3$).

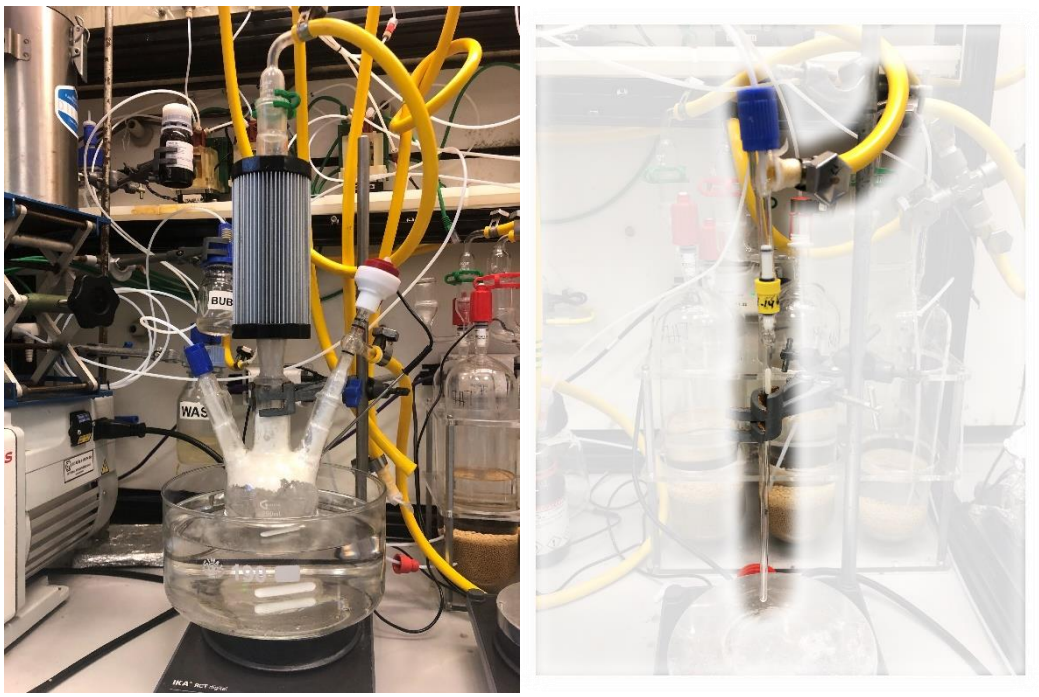


Figure S13: (A) Setup of $CeOTf_3$ synthesis (taken after reaction); (B) Semi-Automated NMR Sampling Analysis.

1.3.6 Hardware Graph for $CeOTf_3$ synthesis

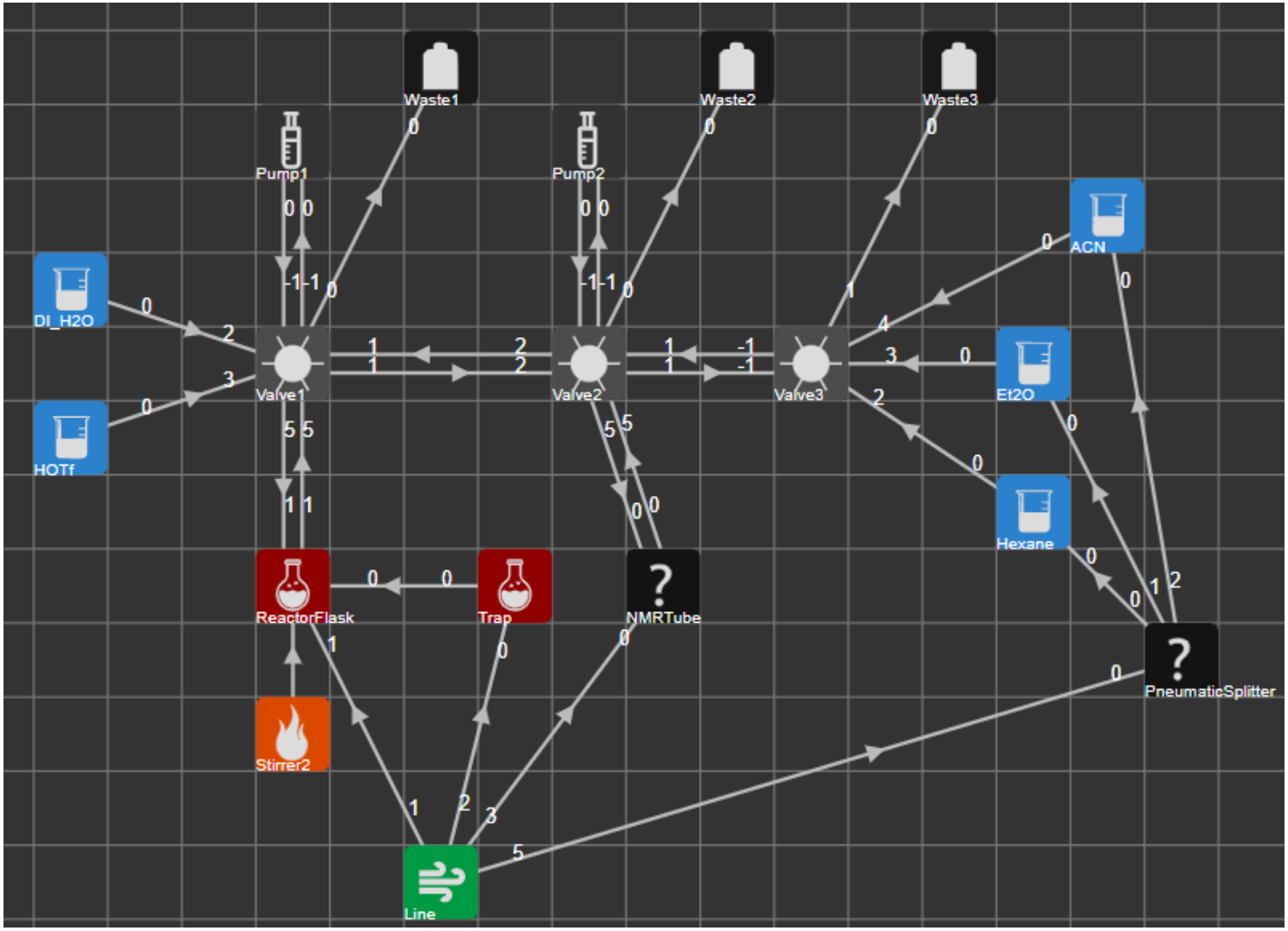


Figure S14: Visual Representation of the hardware graph for the synthesis of $CeOTf_3$. Full graph file as .json available on https://github.com/croningp and visualisable through https://croningroup.gitlab.io/chemputer/xdlapp/.

1.3.7 XDL – $CeOTf_3$ synthesis

The following is the XDL file executed by the platform in concert with the graph shown above (**Figure S14**). The XDL file has three sections: Hardware, Reagents and Procedure. Comments are added in black for clarity of the reader.

```
<Synthesis>
    <Hardware>
        <Component
        id="PneumaticSplitter"
        type="reactor"
        />
        <Component
        id="Trap"
        type="reactor"
        />
        <Component
        id="ReactorFlask"
        type="reactor"
        />
        <Component
        id="NMRTube"
        type="reactor"
        />
        <Component
        id="HOTf"
        type="Flask"
        />
        <Component
        id="DI_H2O"
        type="Flask"
        />
        <Component
        id="Et2O"
        type="Flask"
        />
        <Component
        id="ACN"
        type="Flask"
        />
        <Component
        id="Hexane"
        type="Flask"
        />
        <Component
        id="Line"
        type="pneumatic_controller"
        />
        <Component
        id="Valve1"
        type='Valve'
        />
        <Component
        id="Valve2"
        type='Valve'
        />
        <Component
        id="Valve3"
        type='Valve'
        />
        <Component
        id="Pump1"
        type='Pump'
        />
        <Component
        id="Pump2"
        type='Pump'
```

```
        />
        <Component
        id="Waste3"
        type='Waste'
        />
        <Component
        id="Waste1"
        type='Waste'
        />
        <Component
        id="Waste2"
        type='Waste'
        />
    </Hardware>

    <Reagents>
        <Reagent
            name='Et2O'
            type='solvent'
        />
        <Reagent
            name='Hexane'
            type='solvent'
        />
        <Reagent
            name='ACN'
            type='solvent'
        />
        <Reagent
            name='DI_H2O'
            type='solvent'
        />
        <Reagent
            name='HOTf'
            type='solution'
        />
        <Reagent
            name='Ce2CO33'
            type='solid'
        />

    </Reagents>

    <Procedure> -
    <!-- Setup Flasks & Solvents -->
    <Confirm
        msg = 'Is Ce2(CO3)3 (1.5 g) loaded into ReactorFlask?'
    />
    <CConnect
        from_vessel = 'ReactorFlask'
        to_vessel = 'Pump1'
    />
    <SchlenkLineTapOpenVacuum
        pneumatic_controller = 'Line'
        port = '1'
    />
    <Wait
        time = '2 mins'
    />
    <!-- EvacuateAndRefill Steps for ReactorFlask and Trap-->

    <Async>
        <EvacuateAndRefill
            vessel='ReactorFlask'
            after_vacuum_wait_time='2 min'
            after_inert_gas_wait_time = '3 min'
            repeats='3'
            gas='high'
        />
    </Async>
    <Async>
        <EvacuateAndRefill
            vessel='PneumaticSplitter'
            after_vacuum_wait_time='2 min'
```

```
        after_inert_gas_wait_time = '3 min'
        repeats='3'
        gas='high'
    />
</Async>
<Wait
    time = '16 mins'
/>
<!-- Begin Reaction -->
<SchlenkLineTapOpenArgon
    pneumatic_controller = 'Line'
    port = '1'
/>
<StartStir
    vessel = 'ReactorFlask'
    stir_speed = '500'
/>
<Transfer
    from_vessel='DI_H2O'
    to_vessel='ReactorFlask'
    aspiration_speed = '15'
    volume = '20 mL'
    from_port = '0'
    to_port = '1'
/>
<Wait
    time = '1 min'
/>
<Confirm
    msg = 'Is HOTf connected to the liquid backbone?'
/>
<Transfer
    from_vessel='HOTf'
    to_vessel='ReactorFlask'
    aspiration_speed = '1'
    volume = '2 mL'
    to_port = '1'
    dispense_speed = '1'
/>
<HeatChillToTemp
    vessel = 'ReactorFlask'
    temp = '100'
    active = 'True'
    continue_heatchill = 'True'
    stir = 'True'
    stir_speed = '500'
/>
<Wait
    time = '18 h'
/>
<HeatChillReturnToRT
    vessel = 'ReactorFlask'
    stir = 'True'
    stir_speed = '250'
/>
<!-- Day 2. Evaporation -->
<Confirm
    msg= 'Is external trap filled with liquid N2?'
/>
<StartStir
    vessel = 'ReactorFlask'
    stir_speed = '500'
/>
<SchlenkLineTapClose
    pneumatic_controller = 'Line'
    port = '1'
/>
<SchlenkLineTapOpenVacuum
    pneumatic_controller = 'Line'
    port = '2'
/>
<SchlenkFlaskTapOpen
    pneumatic_controller = 'Line'
    position = 'top'
```

```
/>
<Wait
    time = '1h'
/>
<SchlenkFlaskTapClose
    pneumatic_controller = 'Line'
    position = 'top'
/>
<SchlenkLineTapClose
    pneumatic_controller = 'Line'
    port = '2'
/>
<!-- Wash solids -->
<SchlenkLineTapOpenArgon
    pneumatic_controller = 'Line'
    port = '1'
/>
<EvacuateAndRefill
    vessel='PneumaticSplitter'
    after_vacuum_wait_time='3 minutes'
    after_inert_gas_wait_time = '1 mins'
    repeats='3'
    gas='high'
/>
<Confirm
    msg = 'Are the solvents connected to the LH backbone'
/>
<ResetHandling
    solvent = 'Et2O'
    volume = '10 ml'
    repeats = '2'
/>
<WashSolid
    vessel= 'ReactorFlask'
    solvent = 'Et2O'
    aspiration_speed = '10'
    volume = '10 mL'
    stir = 'True'
    stir_speed = '500'
    time =' 5 min'
    vacuum_attached = 'False'
    repeats = '4'
/>
<!-- Wash two times with hexanes -->
<ResetHandling
    solvent = 'Hexane'
    volume = '3mL'
    repeats = '3'
/>
<WashSolid
    vessel= 'ReactorFlask'
    solvent = 'Hexane'
    aspiration_speed = '10'
    volume = '10 mL'
    stir = 'True'
    stir_speed = '500'
    time =' 5 min'
    vacuum_attached = 'False'
    repeats = '2'
/>
<SchlenkLineTapOpenVacuum
    pneumatic_controller = 'Line'
    port = '1'
/>
<HeatChill
    vessel = 'ReactorFlask'
    temp = '220'
    time = '36 h'
    stir = 'True'
    stir_speed = '400'
/>
<HeatChillReturnToRT
    vessel = 'ReactorFlask'
    stir = 'True'
```

```
        stir_speed = '250'
    /> -->
    <!-- Prep NMR sample -->
    <ResetHandling
        solvent = 'ACN'
        volume = '3 mL'
        repeats = '3'
    />
    <Transfer
        to_vessel = 'ReactorFlask'
        to_port = '1'
        from_vessel = 'ACN'
        from_port = '0'
        volume = '30 mL'
    />
    <StartStir
        vessel = 'ReactorFlask'
        stir_speed = '500'
    />
    <Wait
        time = '10 min'
    />

    <!-- Take NMR sample -->
    <Confirm
        msg = 'NMR tube connected?'
    />
    <CConnect
        from_vessel = 'ReactorFlask'
        to_vessel = 'Pump2'
    />
    <EvacuateAndRefill
        vessel='NMRTube'
        after_vacuum_wait_time='3 minutes'
        after_inert_gas_wait_time = '1 mins'
        repeats='3'
        gas='high'
    />
    <SchlenkLineTapOpenVacuum
        pneumatic_controller = 'Line'
        port = '3'
    />
    <Confirm
        msg = 'Is NMR tube closed under vacuum?'
    />
    <SchlenkLineTapOpenArgon
        pneumatic_controller = 'Line'
        port = '3'
    />
    <Transfer
        from_vessel = 'ReactorFlask'
        from_port = '1'
        to_vessel = 'Waste1'
        to_port = '0'
        volume = '2 mL'
        aspiration_speed = '2'
    />
    <StartStir
        vessel = 'ReactorFlask'
        stir_speed = '400'
    />
    <Transfer
        from_vessel = 'ReactorFlask'
        from_port = '1'
        to_vessel = 'NMRTube'
        to_port = '0'
        volume = '2 mL'
        aspiration_speed = '2'
    />
    <Confirm
        msg = 'Is NMR tube filled?'
    /> -->
    </Procedure>
</Synthesis>
```

1.3.8 Analytical Data for $CeOTf_3$

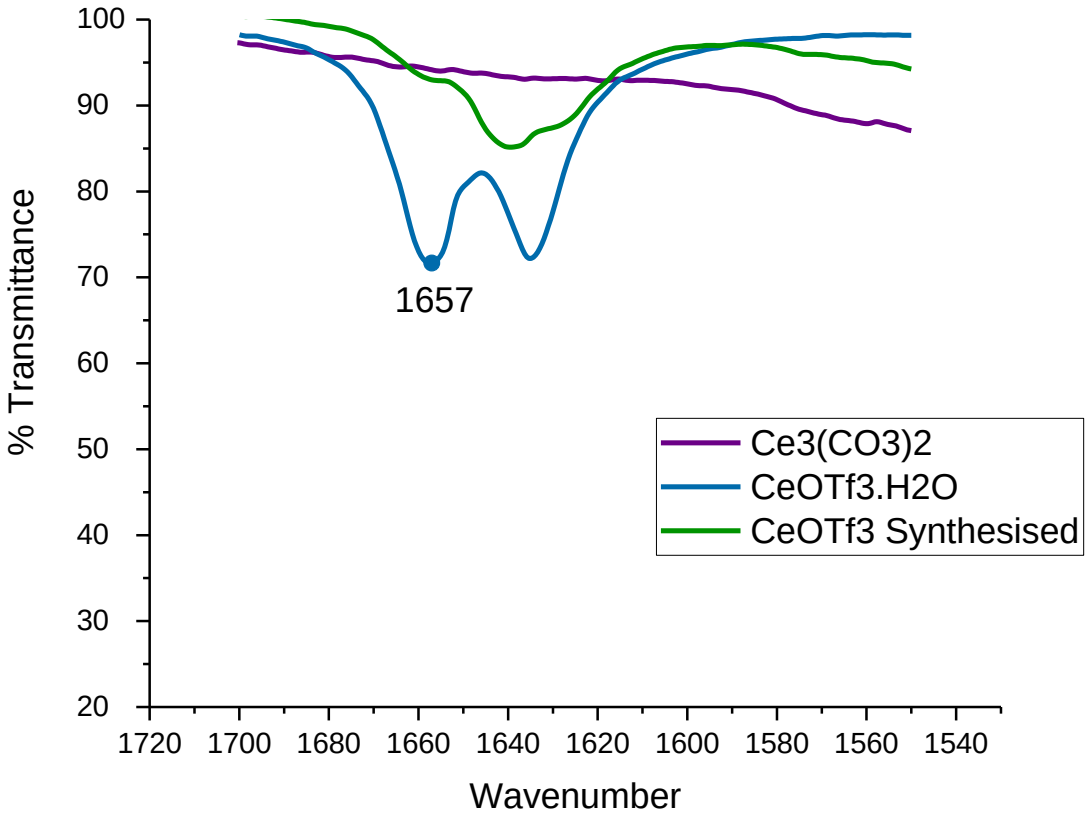


Figure S15: IR Spectrum of synthesised $CeOTf_3$ (green) compared with hydrated $CeOTf_3$ (blue) showing absence of key OH band at 1657 cm^{-1}.

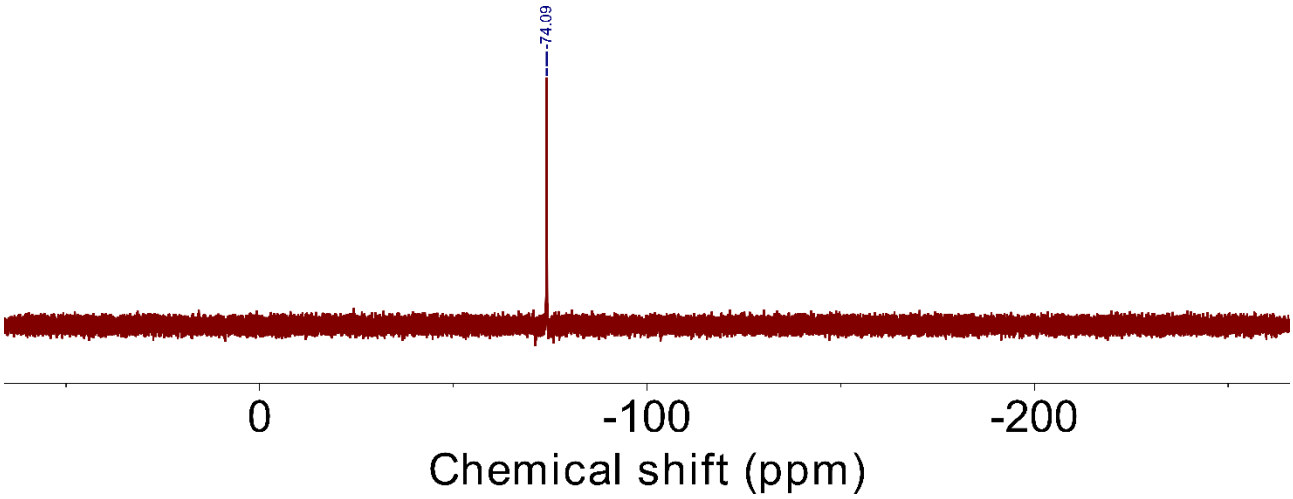


Figure S16: ^{19}F NMR of anhydrous $CeOTf_3$ in H_3-MeCN (w/d_3-MeCN capillary).

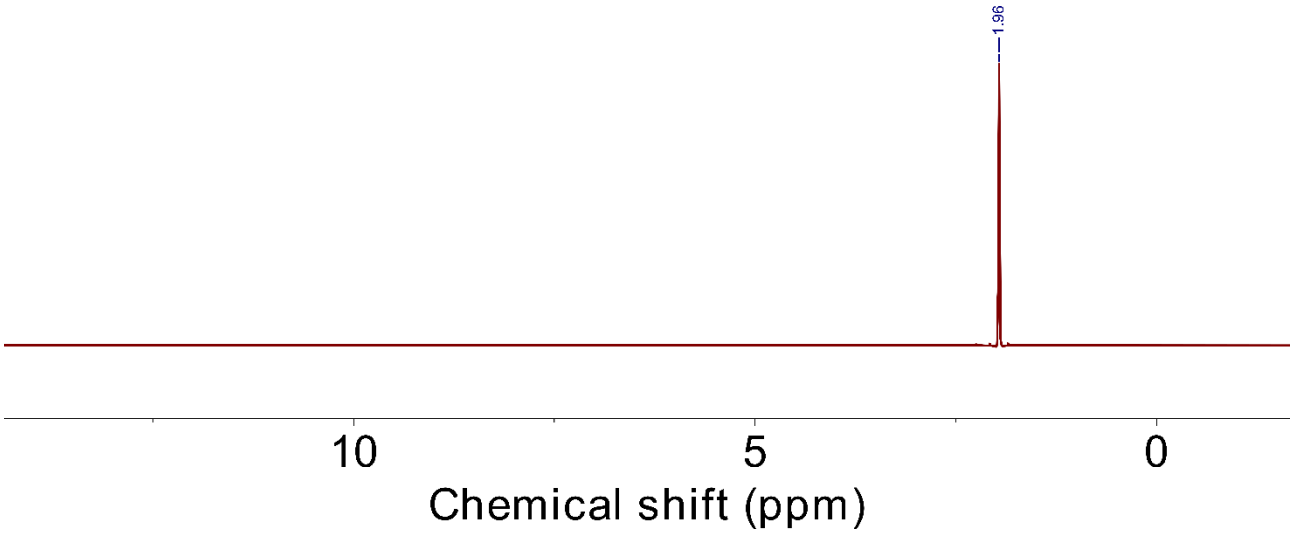


Figure S17: ^{1}H NMR of $CeOTf_3$ in H_3-MeCN (1.96 ppm, w/ d_3-MeCN capillary) showing absense of H_2O (2.13 ppm) and HOTf resonances (br., variable).

1.4 Synthesis of $B(C_6F_5)_3$ (3)

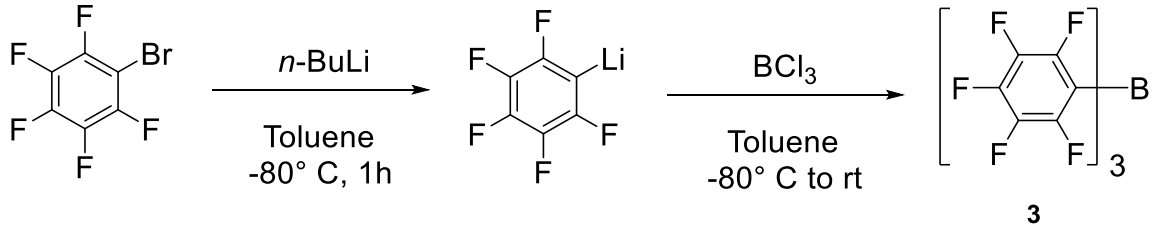


Figure S18: Reaction scheme showing synthesis of compound **3**.

Following an adapted literature procedure,[6] to a stirred solution of bromopentafluorobenzene C_6F_5Br (1.6 mL, 12.8 mmol) in toluene (5 mL), *n*-BuLi (1.6 M in hexanes, 7.8 mL, 0.162 mol) was added dropwise at −80 °C over a period of 7.8 minutes followed by further addition of toluene (5 mL) to ensure complete washing of the *n*-BuLi from the liquid handling tubing. The resulting colourless suspension was stirred for one hour at this temperature. A boron trichloride/*n*-hexane solution (4.2 mL, 1 M, 4.2 mmol) was then added within 50 seconds before further washing of the liquid handling tubing with toluene (5 mL) and the resulting colourless suspension was then slowly warmed to ambient temperature over a period of 90 mins. *In situ* ^{19}F NMR analysis was conducted by transferring 10 mL of the reaction mixture to the NMR machine's flow cell to confirm conversion. The whole solution was then transferred through a frit to a 3-necked round bottomed flask appended on one neck with an inverted Schlenk tube and on a second attached to an independent solvent trap through a remotely operable Lowers Hanique tap (See Fig.s 7 and S22). The solvent was distilled into the cryogenic solvent trap under reduced pressure, resulting in a yellowish residue. The solid residue was sublimed into the inverted Schlenk Flask at 100°C yielding $B(C_6F_5)_3$ (840 mg, 38%) as a colourless, needle-like solid.

Analytical data was consistent with literature values for anhydrous $B(C_6F_5)_3$.[6,7]

^{19}F NMR (C_7H_8, 43 MHz) δ −128.8 (m, 6F), −142.5 (m, 3F), −160.5 (m, 6F) ppm; (C_6D_6, 376 MHz) δ −128.8 (m, 6F), −141.6 (m, 3F), -160.0 (m, 6F) ppm;

^{11}B NMR (C_6D_6, 160 MHz) δ −58.6 (br. s) ppm.

1.4.1 Hardware Graph

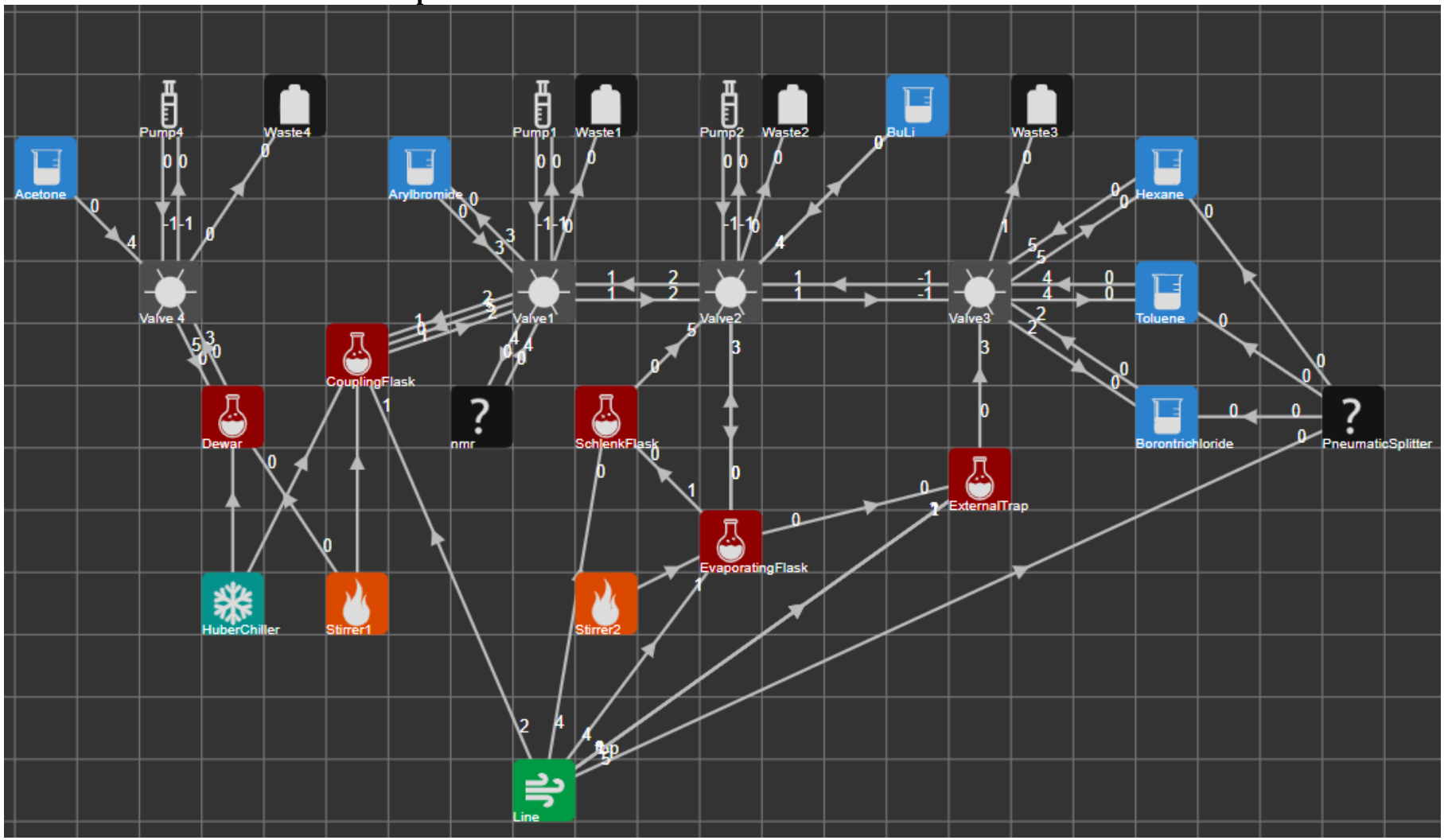


Figure S19: Visual Representation of the hardware graph for the Synthesis of $B(C_6F_5)_3$. Full graph file as .json available on https://github.com/croningp and visualisable through https://croningroup.gitlab.io/chemputer/xdlapp/.

1.4.2 Schlenkputer Hardware Setup

Figure S20: Full setup showing Coupling Flask (LHS) and the Evaporating Flask (RHS), above a paraffin oil bath, which is shown in more detail below.

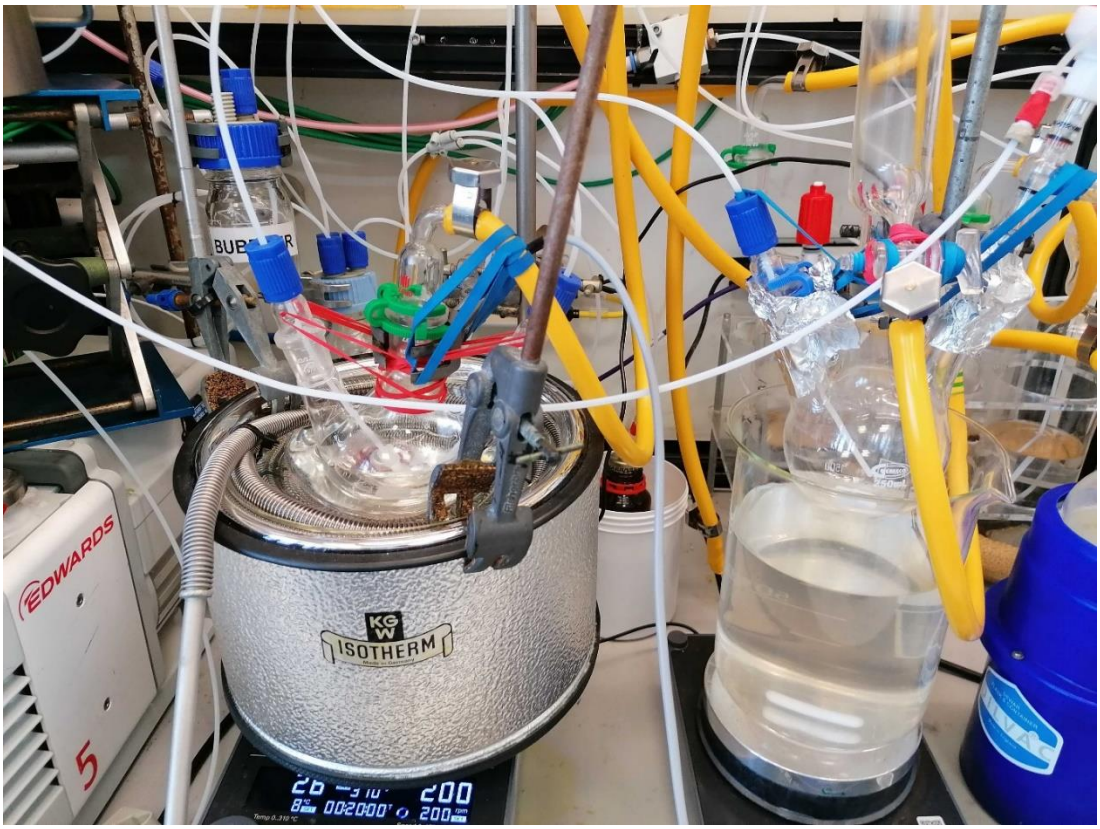


Figure S21: Coupling flask with chiller setup to cool a dewar of acetone.

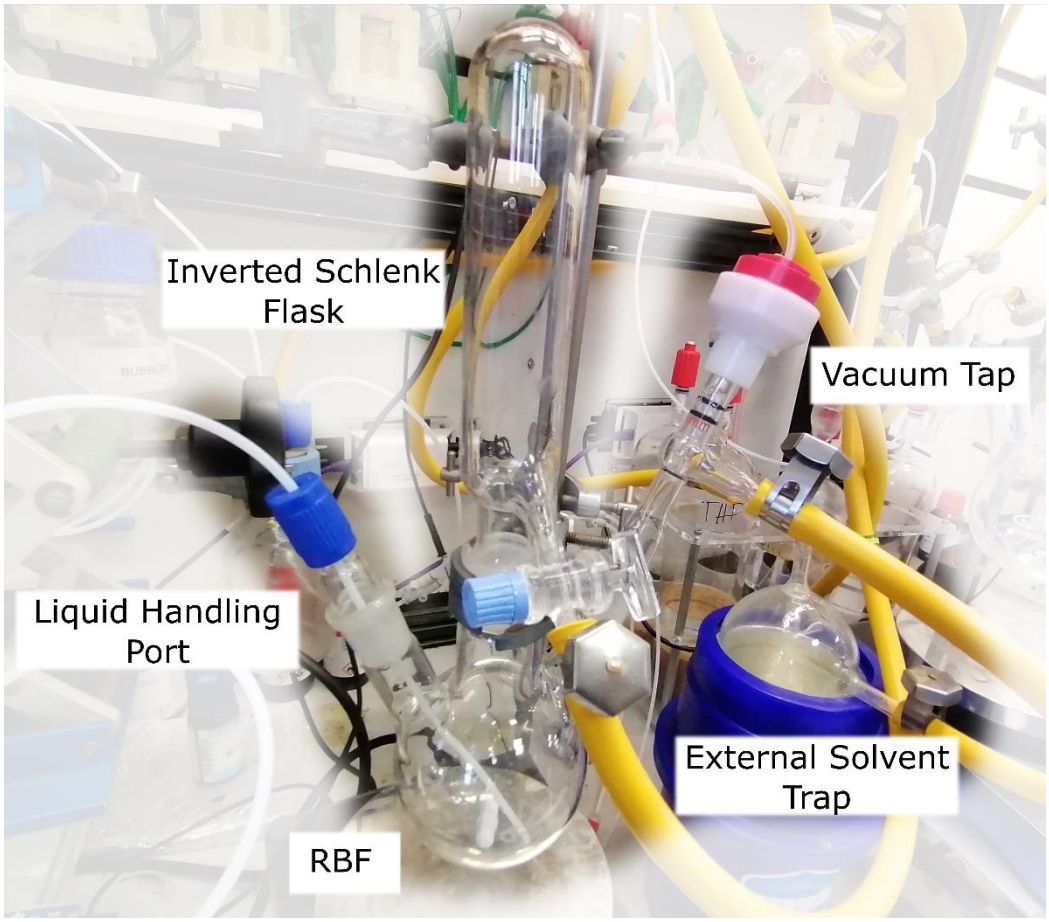


Figure S22: Photograph showing the sublimation setup of the evaporation flask with annotation.

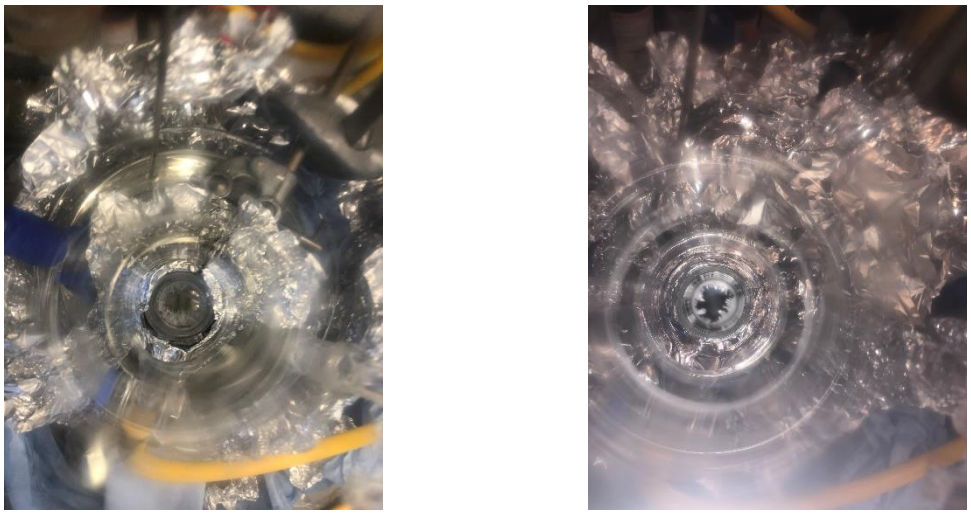


Figure S23: Top down photographs of the sublimate (compound 3) condensing in the inverted Schlenk tube

1.4.3 XDL

The following is the XDL file executed by the platform in concert with the graph shown above (**Figure S19**). The XDL file has three sections: Hardware, Reagents and Procedure. Comments are added in black for clarity of the reader.

```
<Synthesis>

  <Hardware>

    <Component
      id="CouplingFlask"
      type="reactor"
    />
    <Component
      id="PneumaticSplitter"
      type="custom"
    />
    <Component
      id="Toluene"
      type="reagent"
    />
    <Component
      id="EvaporatingFlask"
      type="reactor"
    />
    <Component
      id="ExternalTrap"
      type='reactor'
    />
    <Component
      id="SchlenkFlask"
      type="reactor"
    />
    <Component
      id="nmr"
      type="custom"
    />
    <Component
      id="Line"
      type="pneumatic_controller"
    />
    <Component
      id="HuberChiller"
      type="chiller"
    />
    <Component
      id="Dewar"
      type='reactor'
    />
    <Component
      id="Valve1"
      type='Valve'
    />
  <Component
      id="Valve2"
      type='Valve'
    />
  <Component
      id="Valve3"
      type='Valve'
    />
    <Component
      id="Valve4"
      type='Valve'
    />
    <Component
      id="Pump1"
      type='Pump'
```

```
    />
    <Component
      id="Pump2"
      type='Pump'
    />
    <Component
      id="Pump3"
      type='Pump'
    />
    <Component
      id="Waste3"
      type='Waste'
    />
    <Component
      id="Waste4"
      type='Waste'
    />
    <Component
      id="Waste1"
      type='Waste'
    />
    <Component
      id="Waste2"
      type='Waste'
    />
  </Hardware>

  <Reagents>
    <Reagent
        name='Hexane'
        type='solvent'
    />
    <Reagent
        name='Acetone'
        type='solvent'
    />
  <Reagent
        name='Toluene'
        type='solvent'
    />
  <Reagent
        name='Arylbromide'
        type='reagent'
    />
  <Reagent
        name='Borontrichloride'
        type='reagent'
    />
  <Reagent
        name='BuLi'
        type='reagent'
    />
  </Reagents>

  <Procedure>
    <!-- Setup Flasks & Solvents -->
    <Confirm
        msg = 'Is CouplingFlask Connected?'
    />
    <SchlenkLineTapOpenVacuum
      pneumatic_controller='Line'
      port='2'
    />
    <CConnect
        from_vessel = 'CouplingFlask'
        to_vessel = 'Pump1'
    />
    <Confirm
        msg = 'Is EvaporatingFlask Connected?'
    /> <!-
- When setting up open tap on inverted Schlenk flask so that tubing up to the line is also evacuated. Make su
re N2 does not slightly pop the tap out during the run. This is where elastic bands are best. -->
    <SchlenkLineTapOpenVacuum
      pneumatic_controller='Line'
```

```
      port='4'
    />
    <CConnect
        from_vessel = 'EvaporatingFlask'
        to_vessel = 'Pump2'
    /> -->
    <Wait
        time = '2 min'
    />
    <Async>
        <EvacuateAndRefill
      vessel='CouplingFlask'
      after_vacuum_wait_time='3 minutes'
      repeats='3'
      gas='high'
      />
    </Async>
    <Async>
        <EvacuateAndRefill
      vessel='EvaporatingFlask'
      after_vacuum_wait_time='3 minutes'
      repeats='3'
      gas='high'
      />
    </Async>
    <Async>
        <EvacuateAndRefill
            vessel = 'PneumaticSplitter'
            after_vacuum_wait_time='3 minutes'
        repeats='3'
        gas='high'
        />
    </Async>
    <Wait
        time = '13 mins'
    />


    <!-
- This steps allows us to replace the rotoflow tap on the solvent ampoule with a SubaSeal and Liquid Handling
 Tubing-->
  <Confirm
        msg = 'Are the solvents connected to the liquid handling backbone?'
    />
  <ResetHandling
        solvent='Toluene'
        repeats='3'
        volume='5mL'
    />
    <!-- Begin Reaction -->
  <Add
        reagent='Toluene'
        vessel='CouplingFlask'
        port = '0'
        volume = '13 mL'
        stir = 'true'
        stir_speed = '200'
    />
  <Add
        reagent='Arylbromide'
        vessel='CouplingFlask'
        volume='1.6 mL'
    dispense_speed='20'
        stir = 'true'
        stir_speed='200'
        port = '0'
    />
  <Add
        reagent='Toluene'
        vessel='CouplingFlask'
        port = '0'
        volume = '5 mL'
        dispense_speed='20'
        stir = 'true'
```

```
      stir_speed='200'
  />
  <HeatChillToTemp
      vessel = 'CouplingFlask'
      temp = '-80'
      active = 'True'
      continue_heatchill = 'True'
  />
  <StartStir
    vessel = 'CouplingFlask'
    stir_speed = '400'
  />
<Add
      reagent='BuLi'
      vessel='CouplingFlask'
      volume = '7.8 mL'
      port = '0'
  dispense_speed='1'
      stir_speed = '200'
      stir = 'true'
  />
<Add
      reagent='Toluene'
      vessel='CouplingFlask'
      port = '0'
      volume = '5 mL'
      dispense_speed='1'
      stir_speed = '200'
      stir = 'true'
  />
<Wait
      time = '1h'
  />
<!-- Slow Addition at -80 °C -->
  <Confirm
      msg = 'BCl3 connected to SchlenkLine?'
  />
  <Add
      reagent='Borontrichloride'
      vessel='CouplingFlask'
      volume = '4.2 mL'
      port = '0'
      aspiration_speed = '1'
  dispense_speed='5'
      stir_speed = '200'
  />
<Add
      reagent='Toluene'
      vessel='CouplingFlask'
      port = '0'
      volume = '5 mL'
      dispense_speed='5'
      stir_speed = '200'
  />
  <Wait
      time = '60 min'
  />
  <!--Warm flask to RT by siphoning off cold bath-->
  <Async>
    <Transfer
      from_vessel = 'Dewar'
      to_vessel = 'Waste4'
      volume = '2000'
      aspiration_speed = '100'
      dispense_speed = '100'
    />
  </Async>
  <HeatChillToTemp
      vessel = 'CouplingFlask'
      temp = '10'
      active = 'True'
      continue_heatchill = 'True'
  /> -->
  <Add
```

```
    vessel = 'Dewar'
    reagent = 'Acetone'
    volume = '500'
  />

<!--Cleaning Benchtop NMR-->

  <CleanVessel
      vessel = 'nmr'
      solvent = 'Toluene'
      volume = '10 mL'
      repeats = '3'
  />

<!-- First NMR measurement-->
  <Transfer
      from_vessel = 'CouplingFlask'
      to_vessel = 'nmr'
      volume = '9 mL'
      aspiration_speed = '10'
  />
  <RunNMR
  nmr='nmr'
  protocol='1D FLUORINE+'
  protocol_options="{'Number': 64, 'RepetitionTime': 5, 'AcquisitionTime': 3.2, 'PulseAngle': 90}"
  comment='First Measurement' />
<Transfer
      from_vessel='nmr'
      to_vessel='CouplingFlask'
      volume = '10 mL'
  />

  <!-- Evaporation & Sublimation Steps -->

  <Confirm
      msg = 'Ready for evaporation and sublimation?'
  />

  <SchlenkLineTapOpenVacuum
    pneumatic_controller='Line'
    port='1'
  />
  <StartStir
      vessel = 'EvaporatingFlask'
      stir_speed ='200'
  />
  <Transfer
      from_vessel='CouplingFlask'
      to_vessel='EvaporatingFlask'
      from_port='1'
      aspiration_speed = '1'
      volume = '100 mL'
  />
  <StartStir
      vessel = 'EvaporatingFlask'
      stir_speed ='500'
  />
  <SchlenkLineTapClose
      pneumatic_controller = 'Line'
      port = '4'
  />
  <SchlenkFlaskTapOpen
      pneumatic_controller = 'Line'
      position = 'top'
  />
  <HeatChill
      vessel='EvaporatingFlask'
      temp='40'
      stir='true'
      stir_speed='420'
      time = '30 mins'
  />
  <SchlenkFlaskTapClose
      pneumatic_controller = 'Line'
```

```
        position = 'top'
    />
    <SchlenkLineTapClose
        pneumatic_controller = 'Line'
        port = '1'
    />
    <SchlenkLineTapOpenVacuum
        pneumatic_controller='Line'
        port ='4'
    />
    <Wait
        time = '10 mins'
    />
    <HeatChill
        vessel='EvaporatingFlask'
        temp='120'
        stir='true'
        stir_speed='320'
        time = '3 h'
    />
    <Confirm
        msg = 'Sublimation complete?'
    />
    <SchlenkLineTapOpenArgon
        pneumatic_controller='Line'
        port='4'
    />
    <Confirm
        msg = 'Disconnect Flask and analyse product'
    />
  </Procedure>
</Synthesis>
```

1.4.4 NMR Spectra of $B(C_6F_5)_3$.

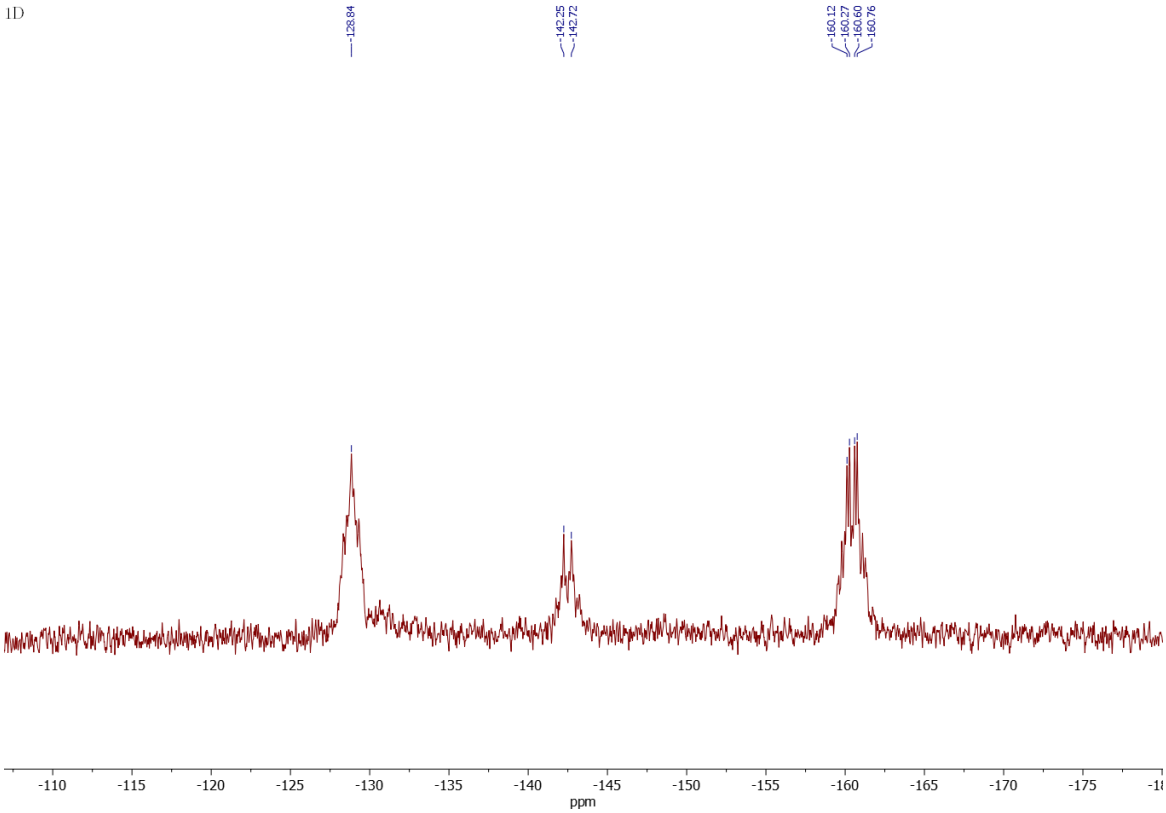


Figure S24: ^{19}F NMR spectrum (43 MHz ^{1}H) of $B(C_6F_5)_3$ before sublimation. Sample prepared in PhMe and transferred to NMR flow cell through Schlenkputer liquid handling system.

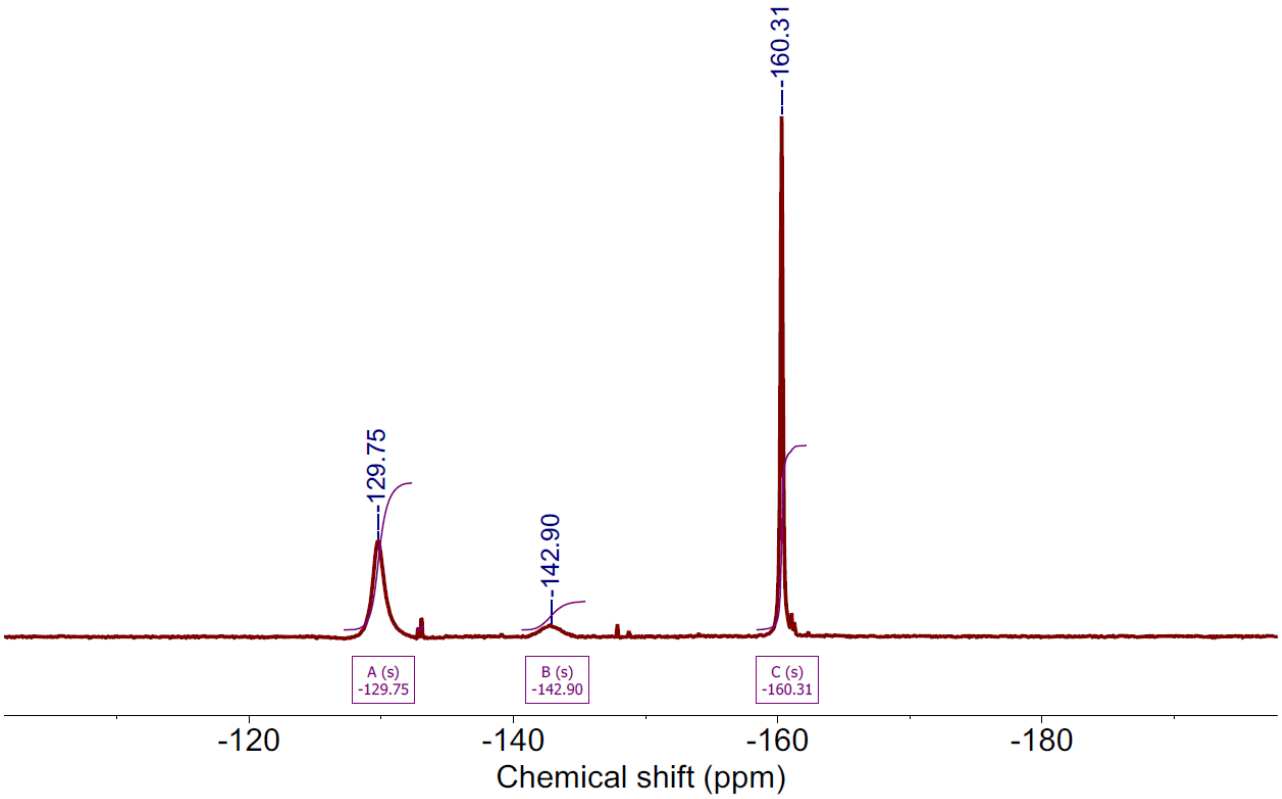


Figure S25: ^{19}F NMR spectrum (376 MHz) of the automatically sublimed product (~98% pure by NMR). Sample prepared in C_6D_6 in Argon filled plastic glovebag.

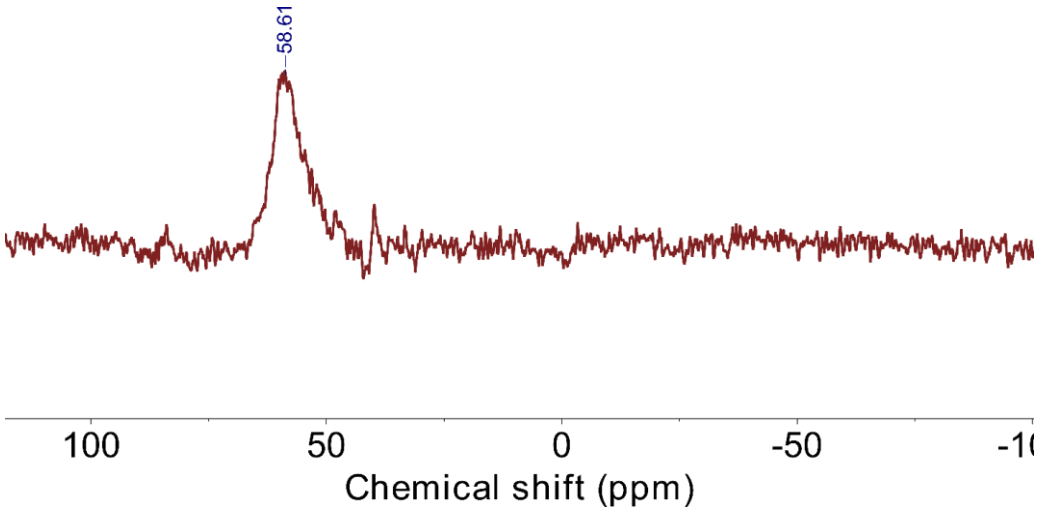


Figure S26: ^{11}B NMR (160 MHz) of automatically sublimed $B(C_6F_5)_3$.

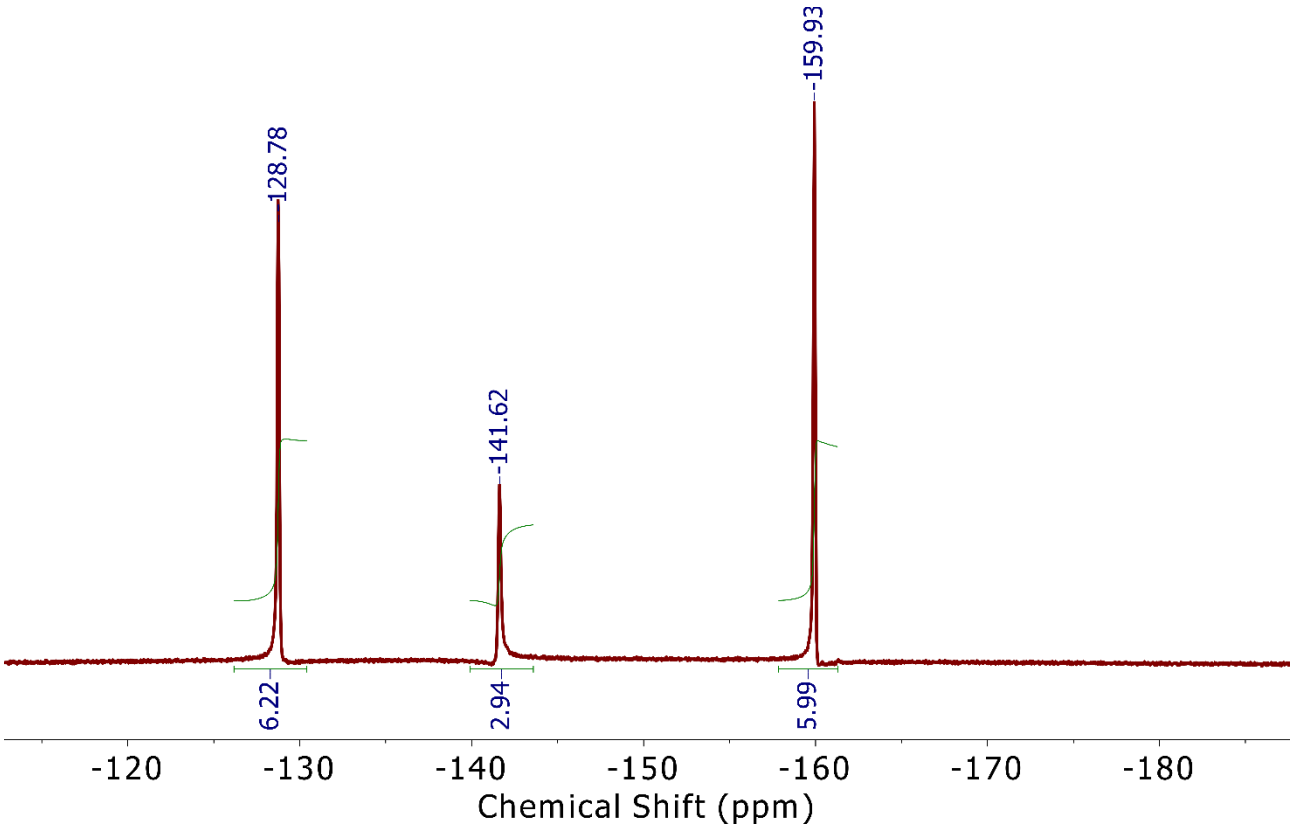
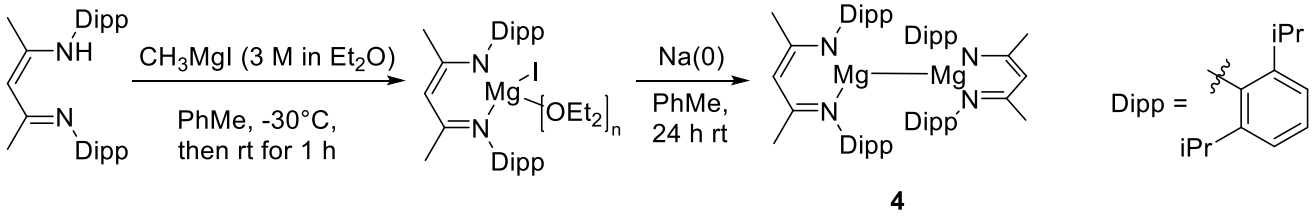


Figure S27: ^{19}F NMR spectrum (C_6D_6) of automatically sublimed $B(C_6F_5)_3$ recrystallised from toluene at −30°C (>99.9% pure by NMR). Prepared in a nitrogen filled glovebox.

1.5 **Synthesis of [(Dipp)NacNac}Mg]$_2$ (4)



4

Figure S28: Reaction scheme of compound **4**.

Starting material ^{Dipp}NacnacH was prepared according to a method reported in literature.[8] Under nitrogen, MeMgI (0.68 mL, 3.0 M in Et_2O, 2.05 mmol) was added to a stirred solution of ^{Dipp}NacnacH (715 mg, 1.71 mmol) in toluene (37 mL) at -30° C. Followed by addition of a further aliquot of toluene (7 mL). The {^{Dipp}NacnacMgI(OEt_2)} solution was allowed to reach room temperature yielding a colourless precipitate. Meanwhile a separate 3-neck round bottom flask, appended with a temperature probe, was charged with a sodium in oil dispersion (ca 9 mL, 40% w/w Na(0)) and washed with hexane (3 x 20 mL) with stirring before addition of the toluene suspension to this flask. This suspension was stirred for 20 h at RT after which time the solution was filtered and the solvent removed yielding a dark residue which was redissolved in hexane, filtered and the solvent removed under reduced pressure to give [(^{Dipp}NacNac)Mg]$_2$ (328 mg, 43%) as a dark yellow solid. A solution of isopropanol (15% in toluene) was added slowly to the flask containing Na(0), maintaining the temperature below 50°C in 0.25 mL aliquots. The temperature change with different aliquot addition volumes (0.1-0.5 mL between temperature readings) was recorded for different experiments and is shown in Fig. 8 in the MS. NMR data was consistent with literature values for compound **4**.[9]

^{1}H NMR (C_6D_6, 400 MHz) δ 7.07 (m, 12H, m-CH_{Ar} & p-CH_{Ar}), 4.82 (s, 2H, NC(C*H*)CN), 3.07 (sept., 8H, C*H*(CH_3)$_2$), 1.54 (s, 12H, NC(CH_3)), 1.16 (d, 24H, (CH_3)CH(CH_3)), 0.98 (d, 24H, (CH_3)CH(CH_3)); (d_8-THF, 400 MHz, recrystallised) δ 7.00 (m, 12H, m-CH_{Ar} & p-CH_{Ar}), 4.70 (s, 2H, NC(C*H*)CN), 3.19 (sept., 8H, C*H*(CH_3)$_2$), 1.55 (s, 12H, NC(CH_3)), 1.05 (dd, 48H, CH(CH_3)$_2$).

Analytically pure crystals for XRD analysis and d_8-THF NMR were grown from slow cooling of a hexane solution to −30°C in a glovebox freezer and the unit cell was confirmed to match the previously reported species [(^{Dipp}NacNac)Mg]$_2$.[9]

1.5.1 Hardware Graph

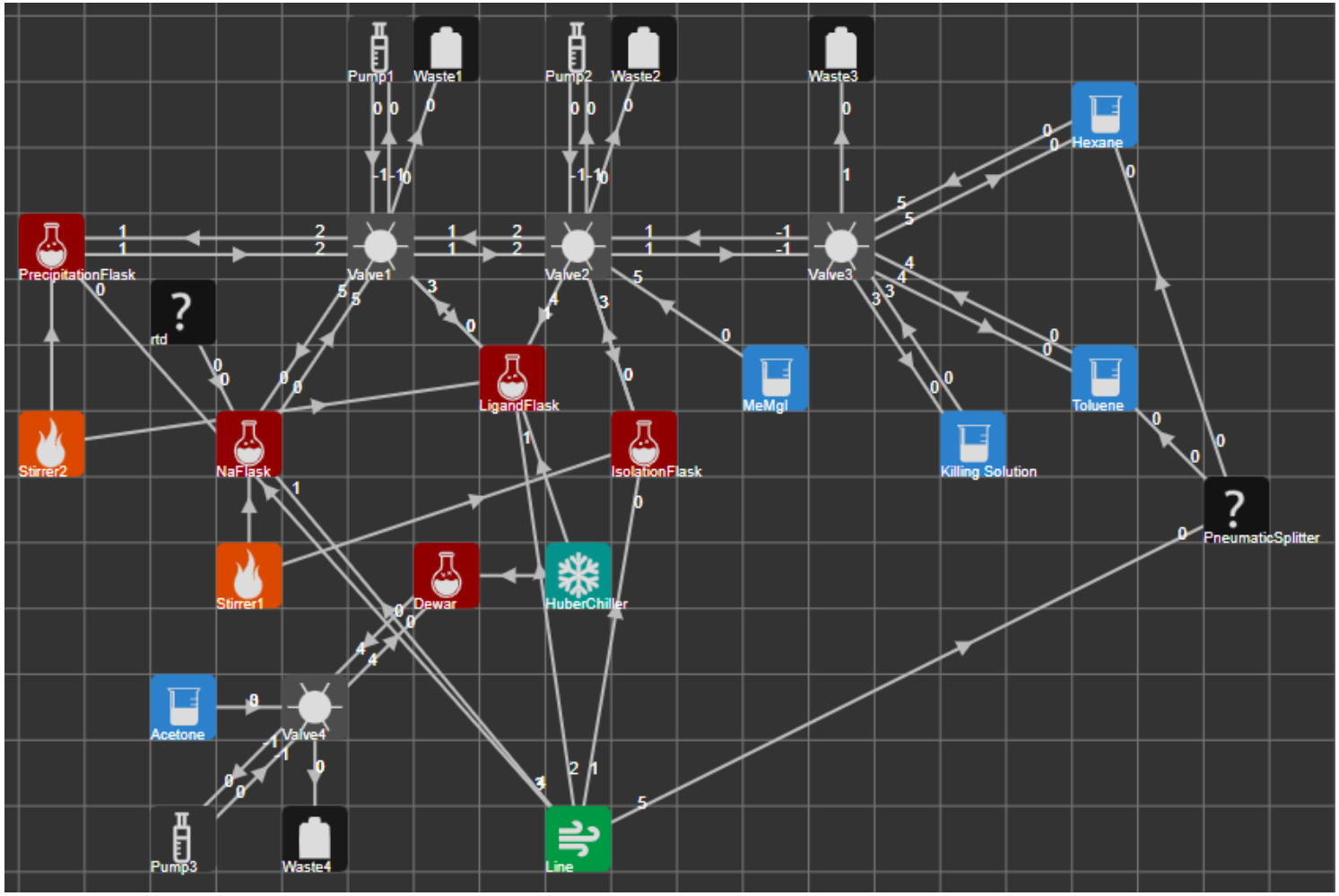


Figure S29: Visual Representation of the hardware graph for synthesis of [(Dipp)NacNac}Mg]$_2$. Full graph file as .json available on https://github.com/croningp and visualisable through https://croningroup.gitlab.io/chemputer/xdlapp/.

1.5.1 XDL

The following is the XDL file executed by the platform in concert with the graph shown above (**Figure S29**). The XDL file has three sections: Hardware, Reagents and Procedure. Comments are added in black for clarity of the reader.

```
<Synthesis>

  <Hardware>

    <Component
      id="LigandFlask"
      type="reactor"
    />
    <Component
      id="PneumaticSplitter"
      type="reactor"
    />
    <Component
      id="NaFlask"
      type="reactor"
    />
     <Component
      id="IsolationFlask"
      type="reactor"
    />
    <Component
      id="PrecipitationFlask"
      type="reactor"
    />
    <Component
      id="HuberChiller"
      type="chiller"
    />
    <Component
      id="Dewar"
      type='reactor'
    />
    <Component
      id="Line"
      type="pneumatic_controller"
    />
    <Component
      id="Valve1"
      type='Valve'
    />
    <Component
      id="Valve2"
      type='Valve'
    />
    <Component
      id="Valve3"
      type='Valve'
    />
    <Component
      id="Valve4"
      type='Valve'
    />
    <Component
      id="Pump1"
      type='Pump'
    />
    <Component
      id="Pump2"
      type='Pump'
    />
    <Component
      id="Pump3"
      type='Pump'
```

```
    />
    <Component
      id="Waste4"
      type='Waste'
    />
    <Component
      id="Waste3"
      type='Waste'
    />
    <Component
      id="Waste1"
      type='Waste'
    />
    <Component
      id="Waste2"
      type='Waste'
    />
  </Hardware>

  <Reagents>
    <Reagent
        name='Toluene'
        type='solvent'
    />
    <Reagent
        name='Acetone'
        type='solvent'
    />
    <Reagent
        name='Hexane'
        type='solvent'
    />
    <Reagent
        name='Killing Solution'
        type='reagent'
    />
    <Reagent
        name='MeMgI'
        type='reagent'
    />
    <Reagent
        name='Na dispersion in oil'
        type='reagent'
    />
    <Reagent
        name='NacNac'
        type='reagent'
    />
  </Reagents>

  <Procedure>

    <!--Reaction Setup-->
    <Confirm
        msg = 'Ligand Flask Setup?'
    />
    <CConnect
            from_vessel = 'LigandFlask'
            to_vessel = 'Pump1'
    />
    <SchlenkLineTapOpenVacuum
        pneumatic_controller = 'Line'
        port = '2'
    />
    <Confirm
        msg = 'Na Flask Setup?'
    />
    <CConnect
        from_vessel = 'NaFlask'
        to_vessel = 'Pump1'
    />
    <SchlenkLineTapOpenVacuum
        pneumatic_controller = 'Line'
        port = '4'
```

```
/>
<Wait
    time = '2 mins'
/>
<StartPurge
    vessel = 'LigandFlask'
/>
<AddSolid
    vessel = 'LigandFlask'
    reagent = 'NacNac'
    mass = '715 mg'
    confirm_solid = 'True'
/>

<StartPurge
    vessel = 'NaFlask'
/>
<AddSolid
    vessel = 'NaFlask'
    reagent = 'Na dispersion in oil'
    mass = '3 g'
    stir = 'True'
    stir_speed = '80'
    confirm_solid = 'True'
/>
<Async>
    <EvacuateAndRefill
        vessel='LigandFlask'
        after_vacuum_wait_time='3 minutes'
        repeats='3'
        gas='high'
    />
</Async>
<Async>
    <EvacuateAndRefill
        vessel='NaFlask'
        after_vacuum_wait_time='3 minutes'
        repeats='3'
        gas='high'
    />
</Async>
<Async>
    <EvacuateAndRefill
        vessel='PneumaticSplitter'
        after_vacuum_wait_time='3 minutes'
        repeats='3'
        gas='high'
    />
</Async>
<Wait
    time = '13 mins'
/>

<Confirm
    msg = 'Are the solvents and MeMgI connected to the liquid handling backbone?'
/>
<ResetHandling
    solvent='Toluene'
    repeats='3'
    volume='5mL'
/>

<!-- Step 1: Magnesiation of the ligand-->

<Add
    reagent='Toluene'
    vessel='LigandFlask'
    port = '1'
    volume = '30 mL'
    stir = 'true'
    stir_speed = '220'
/>
<HeatChillToTemp
    vessel = 'LigandFlask'
```

```
    temp = '-30'
    active = 'True'
    continue_heatchill = 'True'
    stir = 'True'
    stir_speed = '200'
/>
<Add
    reagent='MeMgI'
    vessel='LigandFlask'
    port = '1'
    volume = '0.7 mL'
    stir = 'true'
    stir_speed = '220'
    dispense_speed = '1'
    aspiration_speed = '1'
    prime_n_times = '1'
    priming_volume = '3 ml'

/>
<Add
    reagent='Toluene'
    vessel='LigandFlask'
    port = '1'
    volume = '7 mL'
    stir = 'true'
    stir_speed = '220'
    dispense_speed = '1'
/>


<!-- Step 2: Washing oil from Na dispersion -->
<ResetHandling
    solvent='Hexane'
    repeats='3'
    volume='5mL'
/>
<WashSolid
    vessel = 'NaFlask'
    solvent = 'Hexane'
    volume = '20 mL'
    stir = 'true'
    stir_speed = '80'
    time = '4 min'
    repeats = '3'
    vacuum_attached = 'False'
    aspiration_speed = '5'
/>
<!--Warm flask to RT by siphoning off cold bath-->
<Async>
  <Transfer
    from_vessel = 'Dewar'
    to_vessel = 'NaFlask'
    volume = '2000'
    aspiration_speed = '100'
    dispense_speed = '100'
  />
</Async>
<HeatChillToTemp
    vessel = 'LigandFlask'
    temp = '10'
    active = 'True'
    continue_heatchill = 'True'
/> -->
<Add
  vessel = 'Dewar'
  reagent = 'Acetone'
  volume = '500'
/>


<!-- Step 3: Reduction of NacNacMgI -->
<Add
    reagent='Toluene'
```

```
    vessel='NaFlask'
    port = '1'
    volume = '10 mL'
    stir = 'true'
    stir_speed = '80'
/>
<StartStir
    vessel='NaFlask'
    stir_speed = '80'
/>
<Transfer
    from_vessel='LigandFlask'
    to_vessel='NaFlask'
    aspiration_speed = '5'
    volume = '60 mL'
    rinsing_solvent = 'Toluene'
    rinsing_volume = '5 mL'
    rinsing_repeats = '2'
/>
<Stir
    vessel='NaFlask'
    time = '20 h'
    stir_speed = '400'
/>

<!-- Step 3: Setup Rig for Day 2 -->
<!-- IsolationFlask (see SI) -->
<Confirm
    msg = 'Connected IsolationFlask?'
/>
<SchlenkFlaskTapOpen
    pneumatic_controller = 'Line'
    position = 'top'
/>
<CConnect
    from_vessel = 'IsolationFlask'
    to_vessel = 'Pump2'
/>
<SchlenkLineTapOpenVacuum
    pneumatic_controller = 'Line'
    port = '1'
/>
<Confirm
    msg = 'Connected Precipitation Flask?'
/>
<SchlenkLineTapOpenVacuum
    pneumatic_controller = 'Line'
    port = '3'
/>
<CConnect
    from_vessel = 'PrecipitationFlask'
    to_vessel = 'Pump1'
/>
<Wait
    time = '2 mins'
/>
<Async>
    <EvacuateAndRefill
        vessel='IsolationFlask'
        after_vacuum_wait_time='3 minutes'
        repeats='3'
        gas='high'
    />
</Async>
<Async>
    <EvacuateAndRefill
        vessel='PrecipitationFlask'
        after_vacuum_wait_time='5 minutes'
        repeats='3'
        gas='high'
    />
</Async>
<Async>
    <EvacuateAndRefill
```

```
        vessel='PneumaticSplitter'
        after_vacuum_wait_time='3 minutes'
        repeats='3'
        gas='high'
    />
</Async>
<Wait
    time = '13 mins'
/>
<StartPurge
    vessel = 'NaFlask'
/>
<Confirm
    msg = 'Is toluene connected to the liquid handling backbone?'
/>
<ResetHandling
    solvent='Toluene'
    repeats='3'
    volume='5mL'
/>
<!-- Step 3: Isolate reduced species -->

<StopStir
    vessel = 'NaFlask'
/>
<StartStir
    vessel = 'PrecipitationFlask'
    stir_speed = '220'
/>
<Transfer
    from_vessel='NaFlask'
    from_port = '0'
    to_vessel='PrecipitationFlask'
    to_port = '1'
    volume = '120 mL'
    aspiration_speed = '5'
/>
<Add
    vessel = 'NaFlask'
    reagent = 'Toluene'
    volume = '30 mL'
    stir = 'true'
    stir_speed='250'
    port='1'
/>
<StartStir
    vessel = 'PrecipitationFlask'
    stir_speed = '400'
/>
<SchlenkLineTapOpenVacuum
   pneumatic_controller = 'Line'
   port = '3'
/>
<Wait
    time = '90 mins'
/>
<SchlenkLineTapOpenArgon
    pneumatic_controller = 'Line'
    port = '3'
/>
<ResetHandling
    solvent='Hexane'
    repeats='3'
    volume='5mL'
/>
<Add
    vessel = 'PrecipitationFlask'
    port = '1'
    reagent = 'Hexane'
    volume = '15 mL'
    stir = 'true'
    stir_speed = '180'
/>
<Stir
```

```
        vessel='PrecipitationFlask'
        time = '10 mins'
        stir_speed = '250'
    />
    <Transfer
        from_vessel = 'PrecipitationFlask'
        from_port = '1'
        to_vessel = 'IsolationFlask'
        to_port = '0'
        volume = '30 mL'
        aspiration_speed = '5'
    />
    <Wait
        time = '2 mins'
    />
    <SchlenkLineTapOpenVacuum
        pneumatic_controller = 'Line'
        port = '1'
    />
    <Wait
        time = '60 mins'
    />
    <SchlenkFlaskTapClose
        pneumatic_controller = 'Line'
        position = 'top'
    />

    <!-- Quench Na(0) with 15% iPrOH in Toluene -->

    <Confirm
        msg = 'Product dry and Killing solution connected?'
    />
    <SchlenkLineTapOpenArgon
        pneumatic_controller = 'Line'
        port = '1'
    />

    <AddDynamic
        vessel = 'NaFlask'
        reagent = 'Killing Solution'
        volume = '25 mL'
        sensor = "rtd"
        max_temp = "50"
        wait_after_reading = "1"
        safety_margin = "10"
        aliquot_volume = "0.25 mL"
        stir = 'true'
        stir_speed = '90'
    />
    <Stir
        vessel = 'NaFlask'
        time = '1h'
        stir_speed = '200'
    />
    </Procedure>
</Synthesis>
```

1.5.2 NMR Data for [(^{Dipp}NacNac)Mg]$_2$ (4)

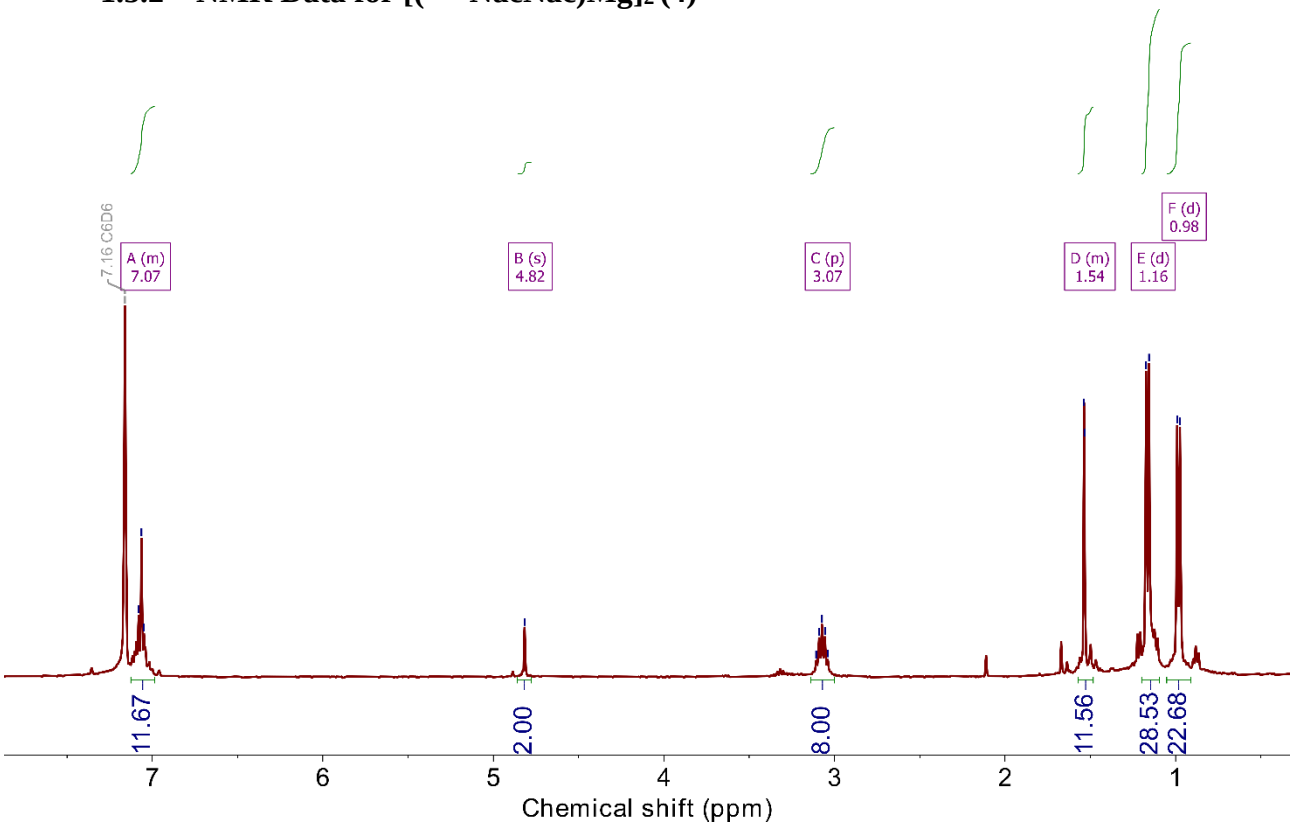


Figure S30: ^{1}H NMR of crude **[(^{Dipp}NacNac)Mg]$_2$ (4)** in C_6D_6 isolated from automated synthesis corresponding to literature values for the same compound. Sample prepared in nitrogen filled glovebox.

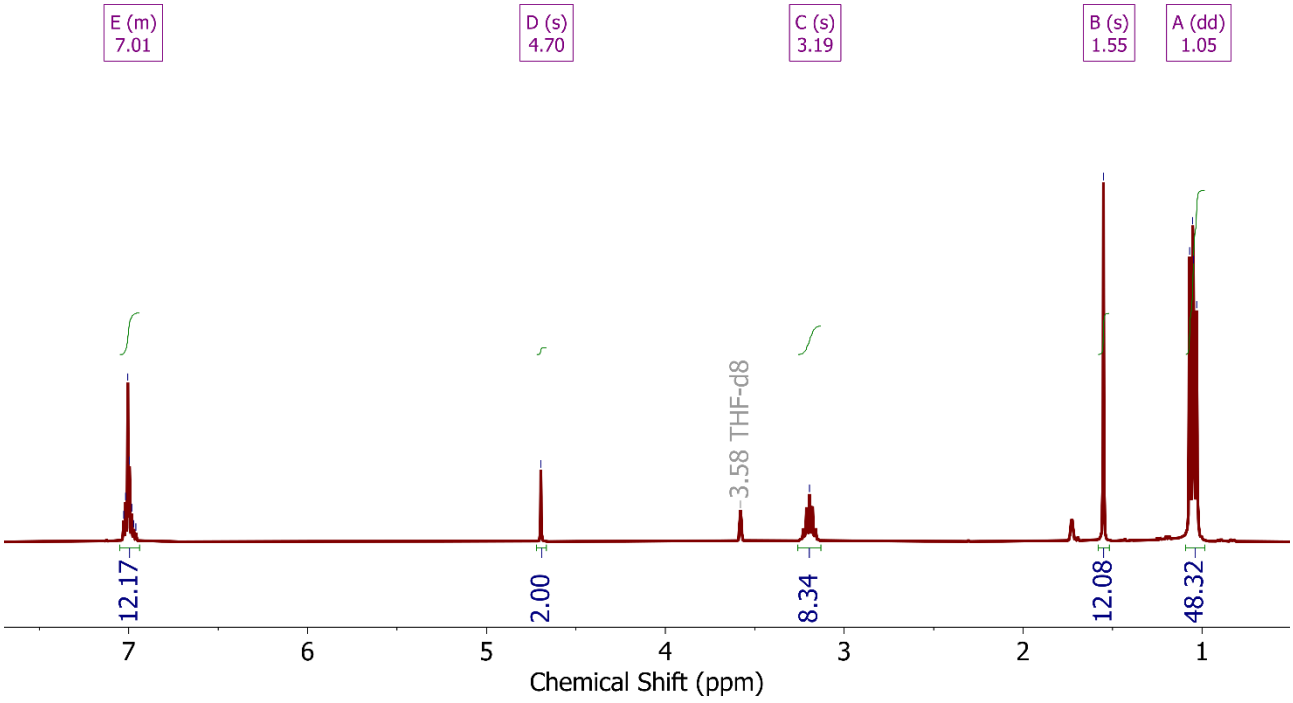


Figure S31: ^{1}H NMR of recrystallised **[(^{Dipp}NacNac)Mg]$_2$ (4)** measured in d_8-THF. Sample prepared in nitrogen filled glovebox.

2 Hardware

2.1 AutoSchlenk Line

Table S1: Bill of Materials for AutoSchlenk Line build

CHEMPU PART NO.	PART DESCRIPTION	SUPPLIER	ORDER CODE	QUANTITY
	Vacutap 1-way bore 9mm, side arm standard /automated	Louwers Hanique	LH10405500	10
	DURAN® Threaded Sockets, reinforced, NS 19/26	DWK Life Sciences / VWR	286581909	4
	DURAN® Threaded Sockets, reinforced, NS 34/35	DWK Life Sciences / VWR	286583404	1
	Smiths Medical™ Portex™ Yellow PVC Tubing 6.4 mm 800/021/300/706	VWR / Smiths Medical	13120873	1 x 30 m
	Edwards Rotary Vane Pump	Edwards	A65301903	1
	ADC Active Digital Controller	Edwards	D39590000	1
	3M Cable Assembly	Edwards	D40001030	1
	APG100-XLC Active linear Pirani vacuum gauge	Edwards	D02604000	1
	2m Line cord with UK plug for Microstar Compact Water Vapor Pump	Edwards	D40013025	1
	NW25 Nozzle Aluminium	Edwards	C10514645	1
	NW25 Centring Ring	Edwards	C10514395	1
	NW25 Clamping Ring Stainless Steel	Edwards	C1051440	1
	Adapter Flange KFGroundCone Stainless Steel, DN 25 KF NS 19/26 joint.	Fisher	10550453	1
	Idex Quick Connect Adapter UPP678	Fisher	05700367	10
	Masterflex Fitting, PVDF, Straight, Female Luer to Hose Barb Adapter, 3/32"; 25/P	Cole Palmer	UY-45512-02	10
	Idex XP-315 Flangeless Fitting, Standard Knurl, Natural ETFE, 1/8" OD Tubing, 1/4-28 Flat-Bottom	Cole Palmer	UY-02020-94	10

Manifold consists of two glass lines each appended with 5 Louwers Hanique Taps through a glass connection providing a hose barb from which to attached Portex tubing to a Schlenk flask. Each line is terminated with a female 19/26 Rodavis joint. The vacuum line (front) is thus connected to a straight J-Youngs tapped joint which allows connection to the Edwards RV5 vacuum pump through a cryogenic trap consisting of a 34/35 Rodavis connection. The gas line is appended on both ends with a straight HP Rotaflo keyed 3mm joint. Finally the RHS terminus of the line is connected to an Edwards Pirani Vacuum Gauge through a Leybold Adapter Flange.

Figure S32: AutoSchlenk glass manifold with 5 ports on each line of vacuum (front) and inert gas (back).

Louwers Hanique taps are connected to the programmable solenoid manifold (see below) with 1/8" PTFE tubing via a Flangeless fitting connected through an Idex Quick connect fitting to a MasterFlex Luer to hose barb connector which allowed connection to the supplier Louwers Hanique tubing.

Figure S33: Assembled AutoSchlenk Line with Liquid N_2 Trap and attached Vacuum pressure gauge.

Figure S1: Additional Photos of manifold build and setting within ChemPU frame.

Waste bottle is connected to the output (RHS) of the gas line, to the ChemPU valve waste output (daisy chained) and subsequently to the bubbler. A long coil of tubing is used between the bubbler and waste bottle to prevent oil suckback.

2.2 Solenoid manifold Build

For build details see the Supplementary Materials associated with Cronin et al., *Nat. Chem.*, 2021 with key differences in the build of this manifold detailed below.[10]

2.2.1 Programmable solenoid manifold

Table S2: Bill of Materials for the programmable solenoid manifold.

PART NO.	PART DESCRIPTION	SUPPLIER	ORDER CODE	QUANTITY
CHEMP0280	Series V100, S41 Type 6-position Manifold	SMC	VV100-S41-06-M5	1
CHEMP0281	3 Port Direct Operated Solenoid Valve - Large flow	SMC	V114A-6LOU	6
CHEMP0282	One-touch Fitting Nickel Plated - 4 mm Hexagon socket head male connector	SMC	KQ2S04-M5N	12
CHEMP0284	One-touch Fitting White Color - 6 mm Male Elbow	SMC	KQ2L06-M5N	3
	One-touch Fitting White Color - 6 mm Male Straight	SMC	KQ2H06-M5A	1
CHEMP0283	One-touch Fitting White Color - 4 mm Male Elbow	SMC	KQ2L04-M5N	7
CHEMP0285	3 Port Direct Operated Solenoid Valve - Large flow - with backplate	SMC	V114A-6LOU-M5	6
CHEMP0286	One-touch Fitting White Color - 6mm -6mm- M5 Male Branch Tee	SMC	KQ2T06-M5A	4
CHEMP0287	One-touch Fitting White Color - 6-6-8 Different Diameter Tee	SMC	KQ2T06-08A	1
CHEMP0338	FEP Fluoropolymer tubing 6mm	RS Components	2550255657	Varies
CHEMP0291	One-touch Fittings Manifold Series - Port A One-touch Fitting, Port B One-touch Fitting	SMC	KM11-04-08-10	1
CHEMP0339	Pneumatic Straight Tube-to-Tube Adapter, Plug In 6 mm	RS Components	771-5614	2
CHEMP0331	M2.5 x 12mm Hex Socket Cap Screw Black, Self-Colour Steel	RS Components	281-653	12
CHEMP0110	M4 x 30mm Cap Head Screws (DIN 912) - A4 Stainless Steel	Accu	SSC-M4-30-A4	4
CHEMP0128	M4 x 10mm Low Head Cap Screws (DIN 7984) - A4 Stainless Steel	RS Components	186-636	
CHEMP0289	Finger Valve 6-6	SMC	VHK3-06F-06F	1
CHEMP0293	In-line Air Filter with One-touch Fitting	SMC	ZFC54-B	1
CHEMP0127	M4 x 10mm Low Head Cap Screws (DIN 7984) - A4 Stainless Steel	Accu	SSCL-M4-10-A4	4
CHEMP0174	D-Link DPE-301GS PoE Splitter	Insight	6338009	1
CHEMP0303	PCB hex spacer 20 mm	RS Components	125-6018	4

CHEMP0309	Rotameter, 0.04-0.5 LPM air, with valve	Omega	FL-2011	1
CHEMP0341	Threaded-to-Tube Elbow Connector Uni 1/8 to Push In 6 mm	RS Components	771-5386	4
CHEMP0311	Rotameter spacer for solenoid manifold	In-house - laser cut	N/A	10
CHEMP0295	Hex socket head cap screw M5x0.80 x 45	Accu	SSCF-M5-45-A4	4
CHEMP0249	M4 x 20mm Penny Washers - A2 Stainless Steel	Accu	HYW-M4-20-A2	4
CHEMP0290	Regulator Single Unit Type	SMC	ARM5SA-08-A	2
CHEMP0294	One-touch Fitting White Color - Different diameter union "Y" 8-6-6	SMC	KQ2U06-08A	1
CHEMP0302	Regulator spacer for solenoid manifold	In-house - laser cut	N/A	6
CHEMP0297	Hex socket head cap screw M3x0.50 x 50 x 18	Accu	SSC-M3-50-A2	2
CHEMP0340	M3 x 16mm Full Thread Cap Head Screws (DIN 912) - A2 Stainless Steel	Accu	SSCF-M3-16-A2	2
CHEMP0342	Non Return Valve, 6mm Tube 6mm Tube, -100 kPa → 1 MPa	RS Components	367-0624	1
CHEMP0088	Polymer Blanking Plug	RS Components	722-047	Varies
CHEMP0308	SMC Cable, Plug, 600mm	RS Components	701-3019	12
CHEMP0035	Arduino Duo with headers	RS Components	769-7412	1
CHEMP0343	M4 x 8mm Socket Button Screws (ISO 7380) - Black A2 Stainless Steel	Accu	SSB-M4-8-A2-BL	4
CHEMP0299	Hex spacer 60 mm	RS Components	664-3303	4
CHEMP0344	M4 x 8mm Vented Socket Cup Point Set / Grub Screws (DIN 916) - Black A2 Stainless Steel	Accu	SSUV-M4-8-A2-BL	4
CHEMP0300	Thumb screw	Accu	SKT-M4-12-A1	4

2.2.2 Build differences from published design

1. Only one Rotameter with flow valve (CHEMP0309) required which is placed on the RHS position of the backplate (Figure S35).

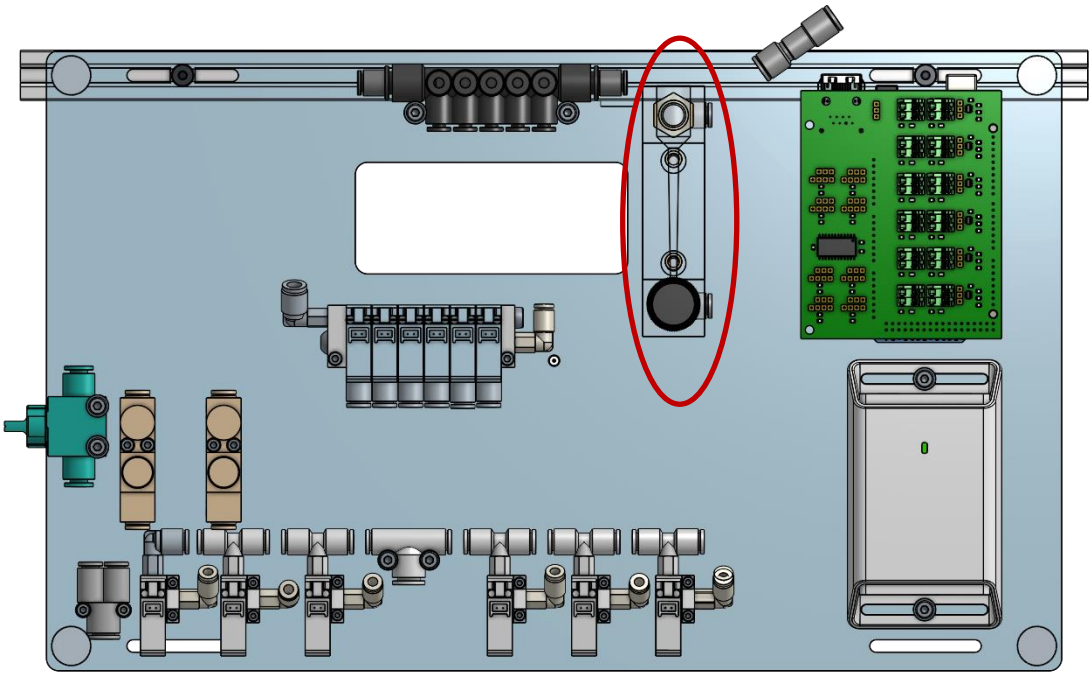


Figure S35: Solenoid manifold Build without tubing showing an upper and lower line of solenoid valves.

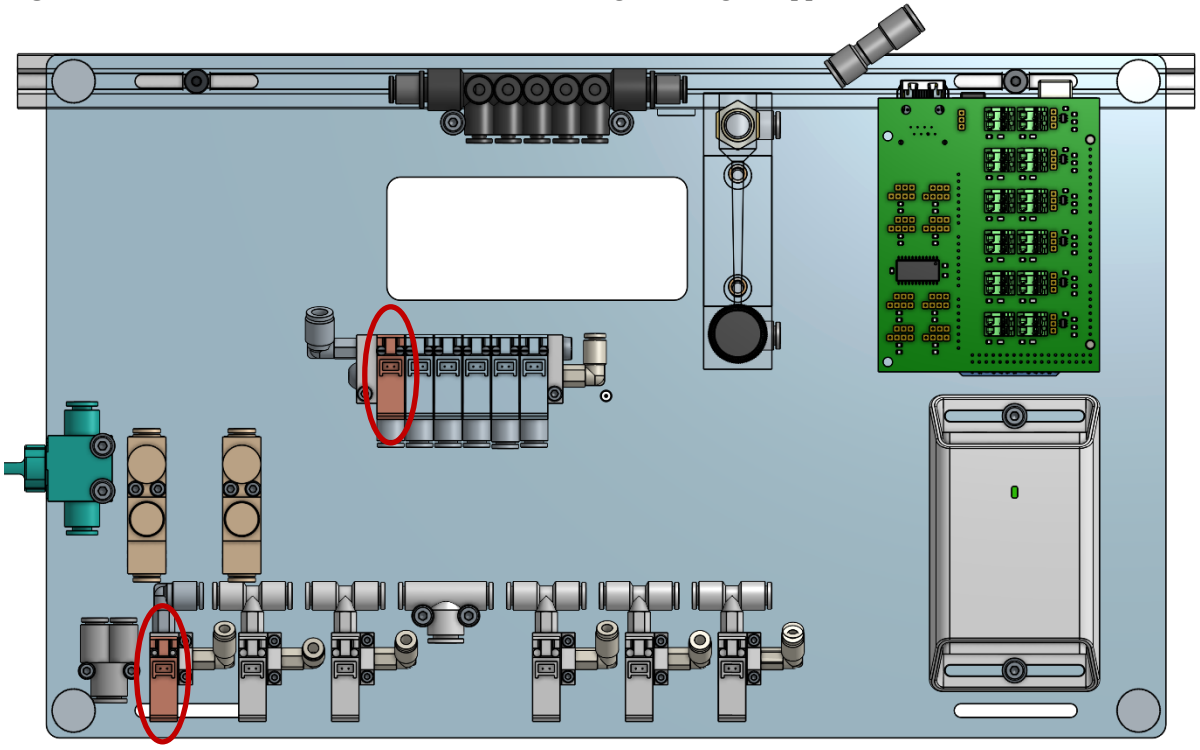


Figure S36: Solenoid manifold with Flask Operating Solenoids highlighted (red). The other 10 solenoids control the AutoSchlenk line with the top set controlling the gas line and the bottom set controlling the vacuum line.

2. Tubing connects directly from left hand regulator (CHEMP0290) to port 3 on manifold (CHEMP0280) via adaptor (CHEMP0284) (Yellow, **Figure S37**). The right hand regulator (CHEMP0290) is connected to the gas distribution manifold (CHEMP0291) via adaptor (CHEMP0339).

3. On the right hand side of the front end manifold the elbow joint (CHEM0284) is replaced with a 3 way joint (CHEMP0286, **Figure S37**, Red Circle). At the same time the RHS Port 1 on the part CHEMP0280 is replaced with a straight fitting (KQ2H06-M5A). This allows connection of the vacuum line (Blue, **Figure S37**) between the two manifolds.

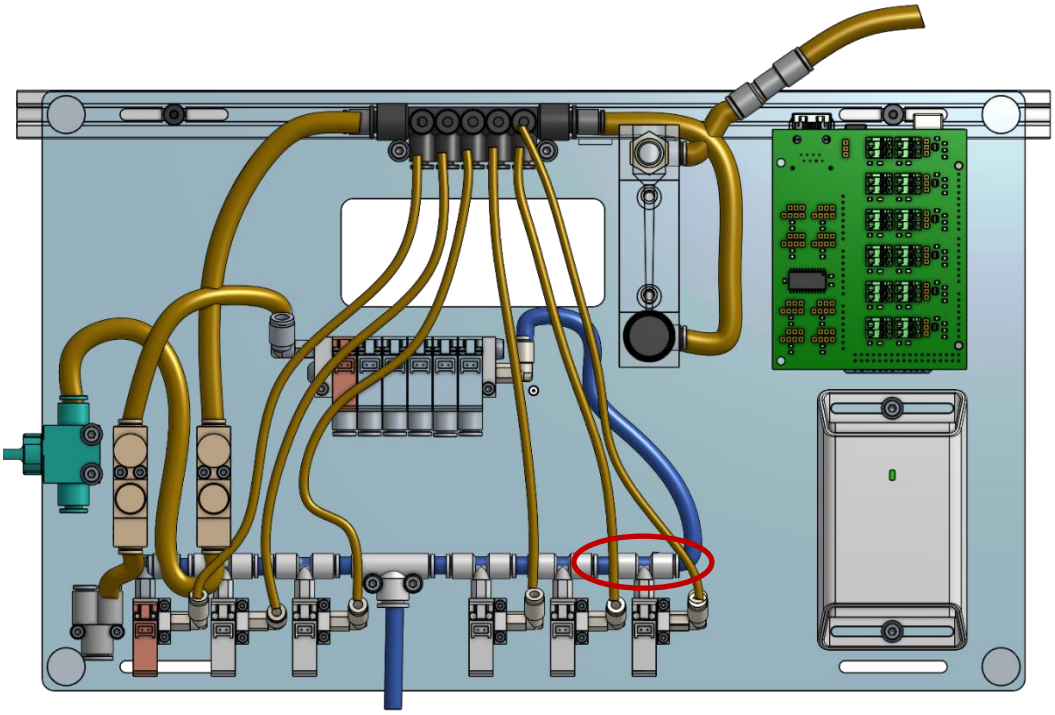


Figure S37: Solenoid manifold with inlet tubing for gas (yellow) and vacuum (blue).

4. Outlet tubing from rotameter connects to gas line on AutoSchlenk manifold via a non-return valve (CHEMP0083) (**Figure S38**).

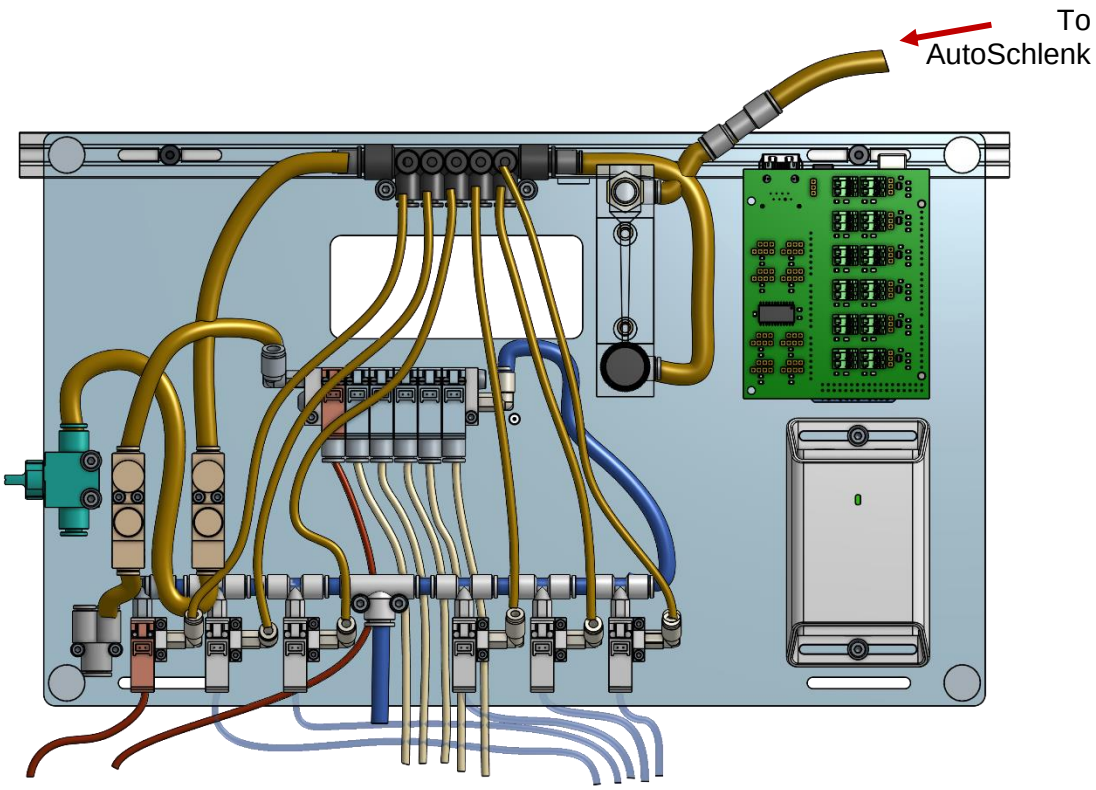


Figure S38: Solenoid manifold with outlet tubing to flasks (red), AutoSchlenk gas line taps (pale yellow/cream), AutoSchlenk Vacuum Line Taps (Pale Blue).

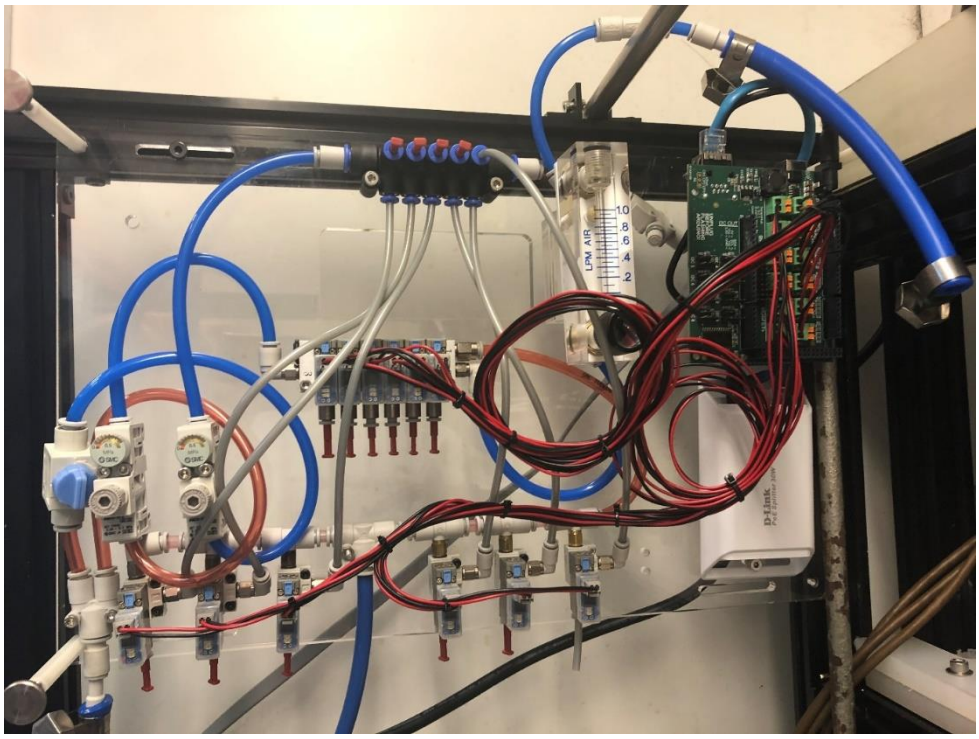


Figure S39: Photograph of the solenoid manifold without outlet tubing as built.

2.3 Glassware Build

2.3.1 Isolation Flask

250 mL RBF appended with a Louwers Hanique Tap. The side arm is also appended with a screw thread joint for a GL14 adaptor and as such can either be connected to Portex tubing (as shown) or directly to liquid handling (see below) depending on the use. The terminal O-ring on the tap was replaced with an FFKM80 O-ring (Barnwell Services, MBMS0085 4.76 mm ID, 1.78 mm thick) to avoid swelling upon solvent exposure.

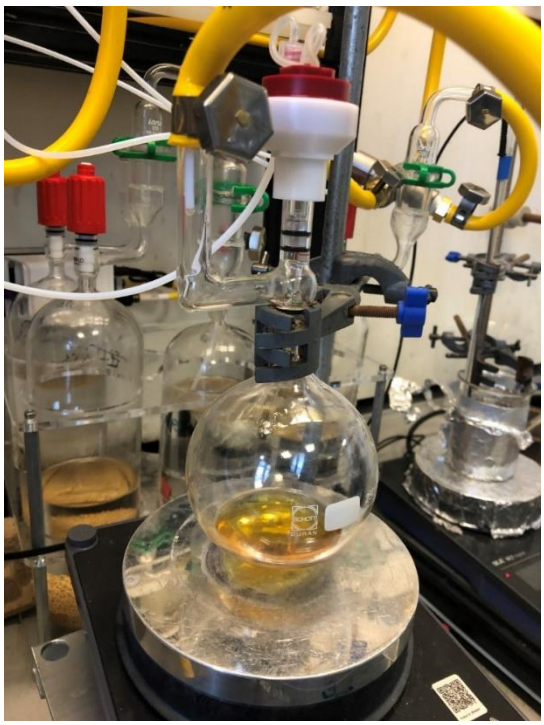


Figure S2: Isolation Flask.

2.3.2 Schlenk (Filter) Flask

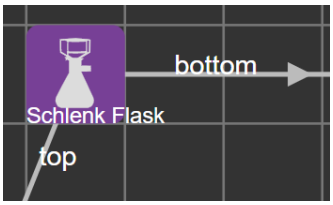


Figure S3: Schlenk Flask.

A medium porosity filter flask is appended with two Louwers Hanique taps on either end. In turn the side arms are appended with GL14 threaded joints for connection to liquid handling system (as shown) or alternately, Portex tubing (see above). The terminal O-rings on both taps are replaced with FFKM80 O-rings (Barnwell Services, MBMS0085 4.76 mm ID, 1.78 mm thick) to avoid swelling upon solvent exposure.

2.4 Other Hardware

2.4.1 Pneumatic Splitter

Figure S4: Pneumatic Splitter

Table S3: Bill of Materials

PART DESCRIPTION	SUPPLIER	ORDER CODE	QUANTITY
Stainless Steel Pipe Fitting, Cross, 3/8 in. Female NPT	Swagelock	SS-6-CS	1
RS PRO Straight Brass Hose Connector, 3/8 in G Male	RS Components	506-7250	4

In order to connect all solvent bottles to the AutoSchlenk system at once the gas/vacuum line was split using a Swagelock 4-way fitting appended with four hose connectors sealed with PTFE tape.

2.4.2 Tube-in-Tube splitter

Table S4: Bill of Materials

PART NO.	PART DESCRIPTION	SUPPLIER	ORDER CODE	QUANTITY
	RS PRO Manifold, G 1/4 Female to G 1/4 Female	RS Components	176-1098	1
	RS PRO Straight Brass Hose Connector, 1/4 in G Male	RS Components	506-7200	2
	RS PRO Thermocouple Compression Fitting for use with Thermocouple With 3.175mm Probe Diameter, 1/4 BSP	RS Components	178-0962	1
	RS PRO NBR G 1/4 Male Blanking Plug	RS Components	176-1049	1

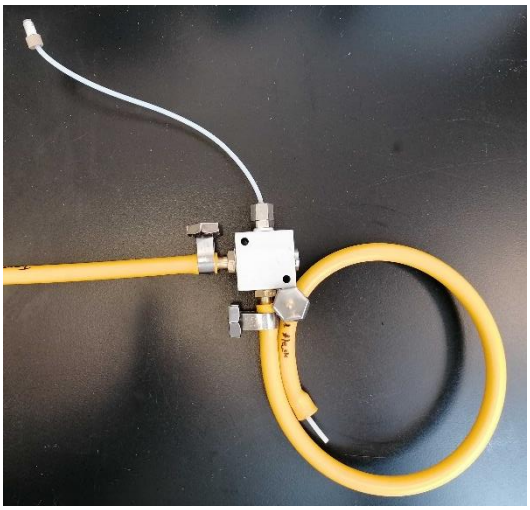


Figure S43: Tube in Tube solvent/gas handling

A 4-way manifold was appended with two brass hose connectors, a blocking plug and a thermocouple compression fitting. The hose connectors were appended with Portex tubing. 1/8” PTFE tubing was threaded through the thermocouple compression fitting and through the Portex tubing until it was slightly longer than the outer tubing and the compression fitting was tightened.

2.4.3 Inline Filters for liquid handling system

Where applicable the use of these is indicated in the .json file for each reaction and is associated with a specific port on a flask meaning the tubing in this port was appended with a filter as shown.

Figure S5: Filter Tip for tubing.

2.5 Benchtop NMR

Spinsolve 43 Carbon from Magritek

- Frequency: 43 MHz Proton
- Resolution: 50% linewidth < 0.5 Hz
- Lineshape: 0.55% linewidth < 20 Hz
- ^{1}H Sensitivity: >120:1 for 1% ethyl benzene
- Dimensions: 58 x 43 x 40 cm
- Weight: 60 kg
- Magnet: Permanent and cryogen free
- Stray field: < 2 G all around system

Figure S45: Spinsolve 43 Carbon benchtop NMR unit with an NMR tube connected to the Schlenkputer liquid handling backbone *via* PTFE tubing.

The instrument is equipped with a flow-cell (Spinsolve SPSFC) to allow online analysis. The cell is fed through the instrument and its location places the NMR tube at the centre of the magnets. Both inlet (bottom) and outlet (top) are connected to 1/8” PTFE tubing with IDEX screw fittings (Figure S45) which is also connected to one of the ChemPU valves. The flow cell allows automatic reaction monitoring in real time by pumping 9 ml of solution from the reaction mixture. In order to inertize the tubing clean, dry solvent (10 mL) is pumped in and out of the flow cell in triplicate before analysis is conducted.

2.6 Temperature Sensor Setup

Table S5: Bill of Materials

PART NO.	PART DESCRIPTION	SUPPLIER	ORDER CODE	QUANTITY
CHEMP0035	Arduino Duo with headers	RS Components	769-7412	1
CHEMP0174	D-Link DPE-301GS PoE Splitter	Insight	6338009	1
	Adafruit PT100 RTD Temperature Sensor Amplifier with MAX31865	Adafruit	3328	1
	Bola Temperature Probe Lemo (PT100)	VWR	P1760-15	1
	Custom Made MOSFET shield	Cronin Group	NA	1

2.6.1 SensorHub

As with the solenoid manifold above our SensorHub system allows communication with the temperature sensors over ethernet. SensorHub consists of an Arduino fitted with a custom-design MOSFET shield (Figure S46) with built-in Ethernet module for control over an IP network (full details on the Arduino firmware, the design of the MOSFET shield and detailed assembly instructions are available on request). Overall, it allows installation of up to 8 analog sensors, 8 sensors with I^2C communication (achieved using an I^2C multiplexer, thus allowing installation of devices with same addresses), several sensors with SPI communication (achieved *via* "software SPI" Arduino feature) and up to 12 PWM devices

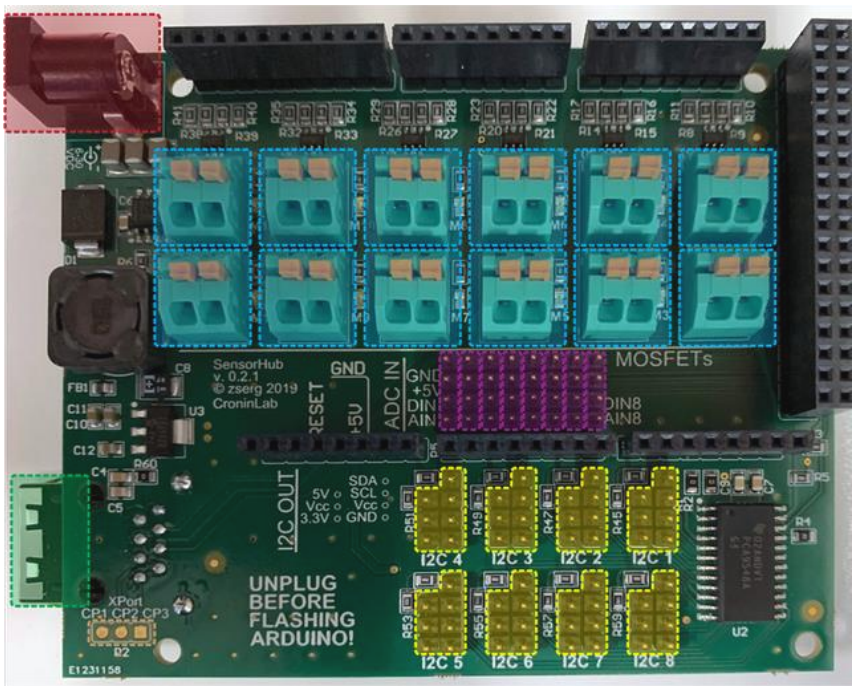


Figure S46: SensorHub board used to power & control temperature sensor.

2.6.2 Reaction temperature sensor (RTD)

The MAX31865 RTD-to-Digital Converter was selected to simplify the interfacing the SensorHub with resistance temperature detector (RTD, or temperature probe). The unit has a built-in 15-bit ADC, input protection, a digital controller, and an SPI-compatible interface. We have selected Adafruit PT100 RTD Temperature Sensor Amplifier as an evaluation board for the MAX31865 converter (**Figure S47**b) and 4-wire PTFE-encapsulated PT100 temperature probe (**Figure S47**a, BOLA, part No. P1750-15) installed *via* screw fitting (BOLA, part No. D629-54 for GL18 glass thread) on the round bottom flask. An installation example is shown below (Figure S48).

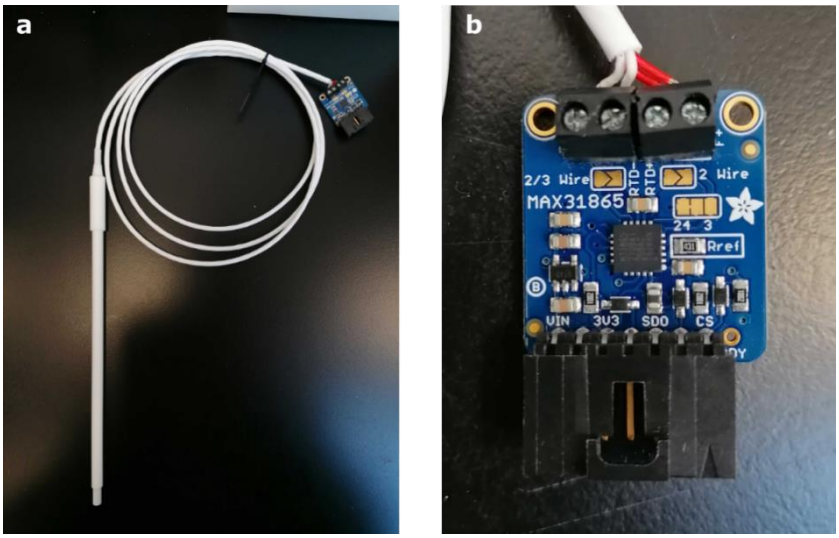


Figure S47: a - PT100 temperature probe connected to **b** – RTD-to-Digital converter.

Figure S48: Example setup of 3-necked RBF with temperature probe.

2.7 Ultra Low Temperature Chiller Setup

Temparature control in the synthesis platform was achieved using a Huber TC 100EF immersion cooling chiller incorporated using an RS232 to USB adaptor. The chiller can achieve temperatures as low as -100°C through automated control. Full details of the code used to control the system can be found at https://github.com/croningp.

After cooling the most efficient reheating method for reactor flasks was found to involve simple siphoning off of the cooling bath solvent, since this most closely mirrors the manual action of removing an RBF from a cooling bath, warming to room temp in ca 90-120 mins. This was achieved using a partitioned pump/valve setup as shown for Pump3/Valve4 in Fig.s S19 & S29.

Figure S6: Huber TC100E immersion cooling chiller.

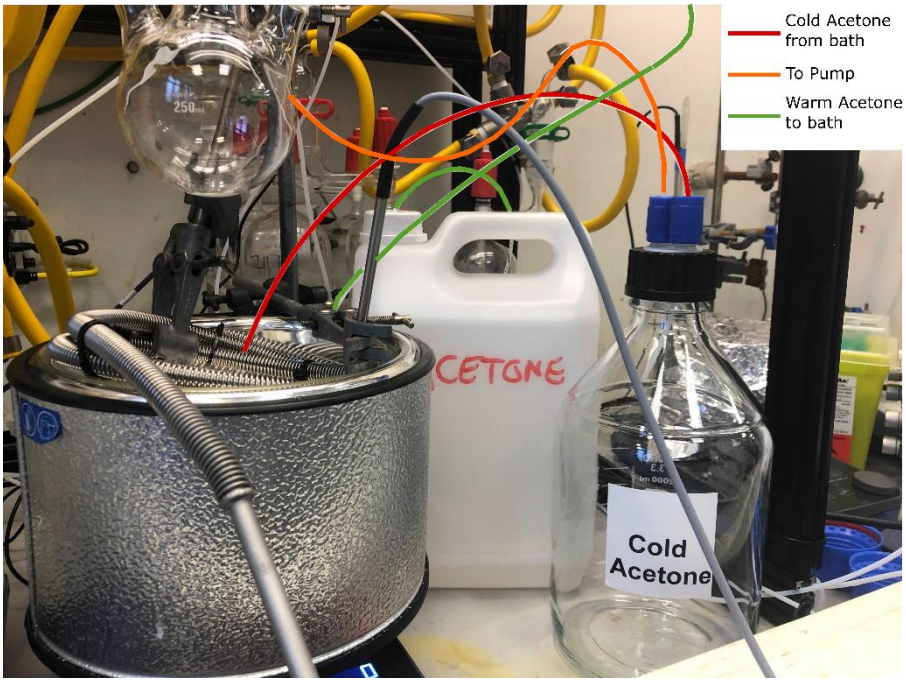


Figure S50: Setup for replacement of acetone cooling bath.

3 Software

3.1 XDL General

All Code associated with this platform and paper, including XDL files as executed, can be found at https://github.com/croningp/Inertputer and is based upon the language outlined in Cronin et al.[11]

3.2 XDL Steps Description

Table S1. χDL synthesis steps implemented in the platform.

Step	Description
Add	Adds given volume of given reagent/solvent to given vessel
AddSolid	Stops run to allow solid to be added manually with user confirmation
Transfer	Transfers solution from one flask to another
StartPurge	Opens Schlenk Line Tap to place flask under a blanket of N_2
EvacuateAndRefil	Sequentially opens and closes vacuum and gas line taps on AutoSchlenk line to cycle and inertise a flask/line
StartStir	Sets stir rate and begins stirring through hotplate
HeatChill	Heat/Chills given cartridge to given temperature for given time
WashSolid	Washes solid in given cartridge by adding solvent and filtering *n* times
CConnect	Turns the valve so that a specific flask has a direct pathway between the flask and pump. Used to evacuate liquid handling system.
ResetHandling	Washes the liquid handling backbone with solvent. Also helps to purge air from valve connections.
Confirm	Takes no action until the user confirms
PrimePumpforAdd	Aspirates 3 mL (default) of reagent into lines to ensure accurate dispensing during add steps.
SchlenkLineTapOpenVacuum	Opens the Louwers Hanique tap on the Vacuum line of the AutoSchlenk line at the defined position.
SchlenkLineTapOpenArgon	Opens the Louwers Hanique tap on the Inert Gas line of the AutoSchlenk line at the defined position.
SchlenkLineTapClose	Closes both Louwers Hanique taps on the AutoSchlenk line at the defined position.
SchlenkFlaskTapOpen	Opens the Louwers Hanique tap on the Inertputer Flask at the defined position.
SchlenkFlaskTapClose	Closes the Louwers Hanique tap on the Inertputer Flask at the defined position.
Async	All commands within Async terms will run concurrently rather than in sequence.

AddDynamic	Add reagent with reference to temperature measurements and within stated safety limits
RunNMR	Engages Spinsolve software to collect spectral data from Magritek Low Field NMR machine.

3.3 New/Custom Graph Nodes

3.3.1 NMR Machine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3.3.2 Pneumatic Splitter


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