

# Autonomous execution of highly reactive chemical transformations in the Schlenkputer

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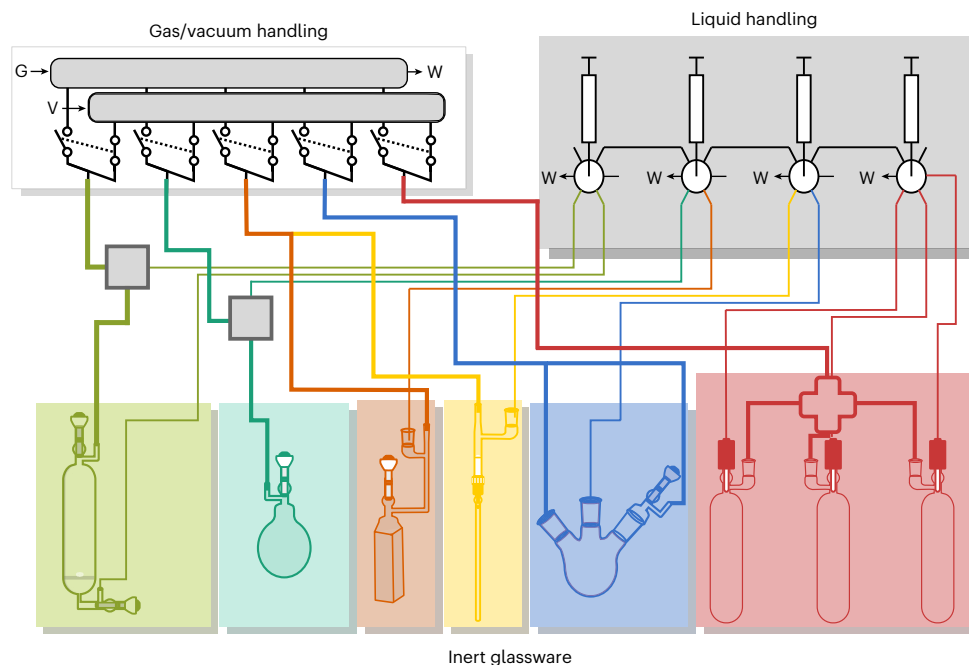
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We design a modular programmable inert-atmosphere Schlenkputer (Schlenk-line computer) for the synthesis and manipulation of highly reactive compounds, including those that are air and moisture sensitive or pyrophoric. Here, to do this, we constructed a programmable Schlenk line using the Chemputer architecture for the inertization of glassware that can achieve a vacuum line pressure of  $1.5 \times 10^{-3}$  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  $H_2O$ . This has enabled automation of a range of common organometallic reaction types for the synthesis of four highly reactive compounds:  $[Cp_2Ti^{III}(MeCN)_2]^+$ ,  $Ce^{III}\{N(SiMe_3)_2\}_3$ ,  $B(C_6F_5)_3$  and  $\{^{Dipp}NacNacMg\}_2$ , which are variously sensitive to temperature, pressure, water and oxygen. Automated crystallization, filtration and sublimation are demonstrated, along with analysis using inline nuclear magnetic resonance or reaction sampling for ultraviolet–visible spectroscopy. Finally, we demonstrate 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.

Automated systems for chemical synthesis, discovery and prediction have the potential to revolutionize the chemical sciences<sup>1</sup>. Bespoke equipment such as peptide synthesizers and preparative high-performance liquid chromatography reduce the level of training, time and discipline-specific skill required for routine tasks, and increase safety by minimizing human contact with toxic reagents. Building on these advances, recently there has been a drive toward more ‘universal’ synthesis machines that can undertake more of the operations automatically with minimal labor<sup>2–4</sup>. Current chemical automation focuses strongly on aerobic transformations, often using liquid handling (LH) systems for low-to-medium-scale synthesis (ca. 0.1–100 g). While some of these systems incorporate basic inert-atmosphere control, these are normally rudimentary and 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 that must be conducted at sub-ppm levels of  $O_2$  and  $H_2O$  (refs. 5–8). An alternative approach involves installing

automated systems inside inert-atmosphere glovebox environments<sup>8,9</sup>, which is ideal for some air-sensitive manipulations (such as weighing solids); however, challenges can arise from working within enclosed systems. These include cross-contamination, rapid solvent evaporation and even oxidation/hydrolysis since the most highly oxophilic and hygroscopic species can readily abstract even sub-ppm quantities of  $O_2$  and  $H_2O$  from a box atmosphere<sup>10–14</sup>. Similarly, reactions under controlled gas environments (such as  $CO$  and  $X_2$ ) 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<sup>8,15</sup>.

Manual inert- and controlled-atmosphere chemistry has, on the other hand, developed largely in the past 50 years due to the increasing availability of technologies such as positive-pressure gloveboxes, Schlenk lines and solvent purification systems<sup>16–19</sup>. In tandem, the ability to investigate and exploit species that react readily under atmospheric conditions has expanded rapidly. However, conducting manipulations



**Fig. 1 | Overview of the Schlenkputer.** The Schlenkputer combines automated liquid handling and gas handling systems in one platform. The 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 adapter, yellow; three-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.

under inert conditions still requires specialist training<sup>20</sup> and many procedures fail due to poor technique<sup>21</sup>. Several key features delineate inert-atmosphere chemistry from traditional bench techniques. Firstly, removal of air from the system by application of vacuum 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<sup>22,23</sup>. This is typically achieved using Schlenk glassware, which has a manually sealable side arm in concert with a Schlenk line or inert manifold that has two distinct lines, one for vacuum and one for inert gas, and several sets of taps that allow connection to the reactors or glassware. After evacuation and refill in triplicate (often known as cycling or inertization), the flasks can be maintained under positive pressure throughout a reaction by retaining connection to the inert gas line on the manifold.

In this Article, we report the design, development and deployment of a fully automated controlled-atmosphere synthesis robot known as the Schlenkputer that can reach reduced pressures of  $1.5 \times 10^{-3}$  mbar and the coupling of this inert-gas handling system with the liquid handling backbone of the Chemputer<sup>2,5</sup> (Fig. 1). Using this system, we demonstrate the complete automated synthesis of a range of sensitive compounds from across the periodic table on a gram scale, including the colorimetric indicator  $Cp_2Ti^{III}(MeCN)_2$  (**1**), readily oxidizable  $Ce^{III}\{N(SiMe_3)_2\}_3$  (**2**), highly moisture-sensitive  $B(C_6F_5)_3$  (**3**) and the alkali metal-reduced  $\{^{Dipp}NaCNacMg\}_2$  (**4**). Using our chemical programming language (XDL)<sup>24</sup>, we remotely program and conduct the synthesis, sampling and analysis of an entire reaction process while maintaining inert conditions. In addition, we demonstrate the incorporation of inline nuclear magnetic resonance (NMR) spectroscopy, temperature sensing for safe quenching of alkali metal reagents and reaction sampling for ultraviolet-visible (UV-vis) analysis.

## Results

### Schlenkputer hardware

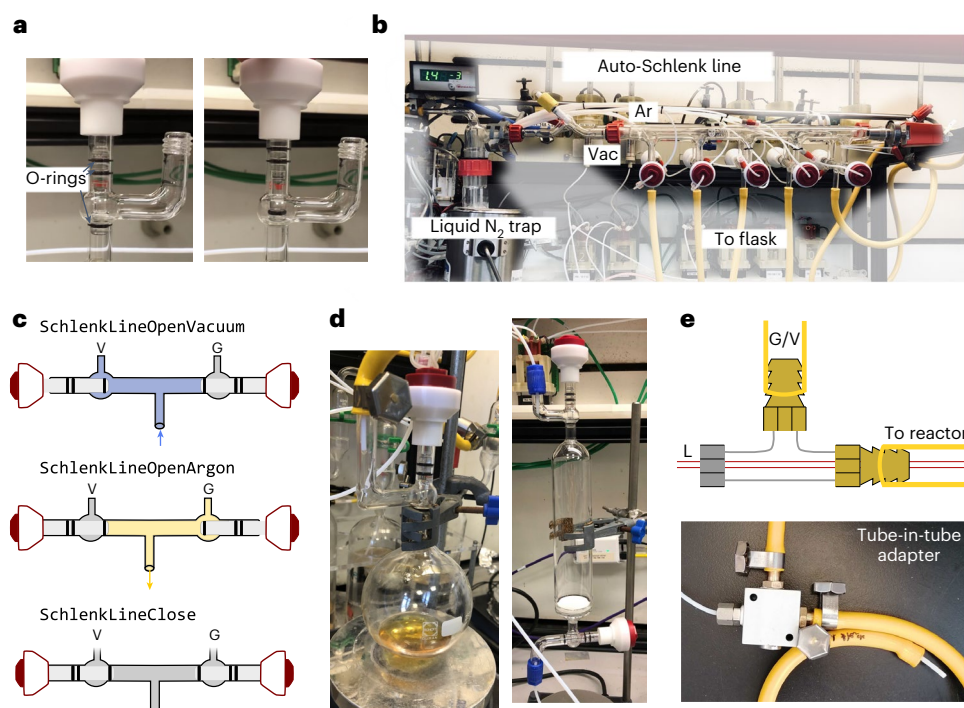
An inert manifold (Schlenk line) consists of an array of taps connecting two gas/vacuum lines to tubing for connection to various flasks and

reactors. To allow for flexibility in conducting manipulations, each tap must be independently operable. Two common Schlenk line tap designs exist: double oblique taps that are rotated to provide a connection between the reactor and the respective manifold lines, or a pair of greaseless stopcocks (such as J Young and Rotaflo) that individually open the reactor to either the vacuum or gas line (or potentially even both if improperly used). We designed a manifold based on the latter style with five reactor lines, thus using ten vacuum taps (that is, five pairs), although we envision this could be easily scaled up to ten reactor lines within the platform described<sup>25</sup>. 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 (Fig. 2a). Three perfluoroelastomer 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 utilizing a programmable solenoid manifold consisting of 12 electromagnetic valves connected to a diaphragm pump and gas lines that, when engaged, were able to affect the opening and closing of each of these taps individually (Supplementary Notes Section 2.2). Our Schlenkputer line, when coupled to a rotary vane pump, can achieve ca.  $1.5 \times 10^{-3}$  mbar pressures and withstand at least 1 bar positive pressure of inert gas (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 min vacuum, 2 min gas and three repeats found to be sufficient for inertization.

### Development of automatically sealable, gas-tight glassware

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



**Fig. 2 | Auto-Schlenk 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.  $1.5 \times 10^{-3}$  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. **d**, Glassware for the Schlenkputer system including an inert-atmosphere isolation flask and inert-atmosphere filter flask. **e**, The tube-in-tube adapter system, which allows liquid and gas handling through one flask port.

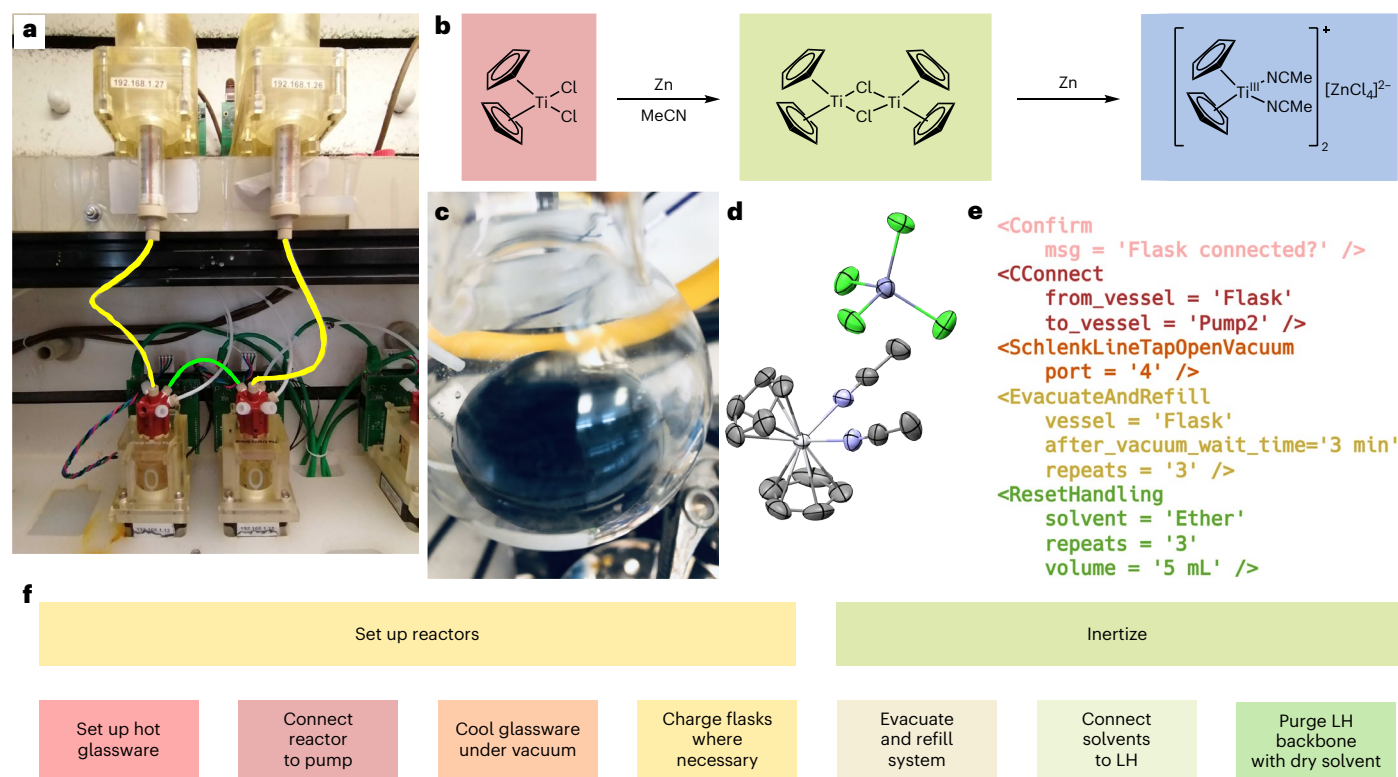
liquid transfer<sup>22,23</sup>. However, our system does not require opening and closing during a reaction and, as such, our inert-atmosphere syntheses can in large part be carried out using commercial Quickfit glassware such as RBFs. Despite this, there is still a need to utilize automated Schlenk-type 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, for example, during crystallization. In addition, there are some operations for which direct opening and closing of connections between reactors may be required.

For these reasons, we developed a set of key pieces of glassware to facilitate the full automation of our reactions (Figs. 1 and 2d). Each flask utilizes the same remotely operable taps as the Schlenk line and is automatically controlled in a similar way. Chemically inert perfluoroelastomer 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 (Fig. 2d, left). A 250 ml RBF with a single automated tap was produced. Solutions of product materials may be transferred into this flask through the liquid handling system and the solvent removed in vacuo, allowing the solid to be retrieved in an inert-atmosphere glovebox. Next, a filtration flask (Fig. 2d, right) was produced, allowing separate inlet and outlet ports for isolation of solids. The large volume allows crystallization 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 during and after reactions. This tap can be used to control the evaporation of solvent/reagents into an external cryogenic trap. 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 utilized for the integration of the gas handling system with the liquid handling backbone of the Chemputer. The simplest involves the use of multinecked glassware fitted with both a liquid handling adapter (B19 to GL14 adapter for 1/8 inch LH tubing) and a gas/vacuum adapter (B24 to 1/4 inch 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. 2d) 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. 2e and Supplementary Fig. 43).

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, red) are connected to the Schlenkputer through a gas line splitter (Supplementary Fig. 42), which means one manifold line can provide all the required solvents with inert gas. The Schlenk filter flask (Figs. 1, green, and 2d, right) is connected through a tube-in-tube adapter on the top port but directly to liquid handling on the bottom, while the Schlenk collection flask (Figs. 1, teal, and 2d, left) only requires a single inlet position to transfer liquids in and to remove the solvents. We have also designed a UV-vis cuvette (Figs. 1, orange, and 4c) and J Young tap NMR tube adapter (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 (Supplementary Fig. 34). This line can also be split to allow an additional inert gas flow over Suba-Seal reagent bottles such as nBuLi.



**Fig. 3 | 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 and green, respectively). **b**, Scheme showing Ti(IV) reduction with indicative solution colors for different stages. **c**, Color of the product solution after passing through the fully inertized LH

backbone. **d**, XRD crystal structure of the isolated product from the automated reaction. **e**, A section of an 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.

This method has several advantages: first, these tube-in-tube adapters can allow for connection of the inert manifold to liquid handling systems that are not designed with inertization in mind or allow the use of non-bespoke glassware; secondly, the adapters 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

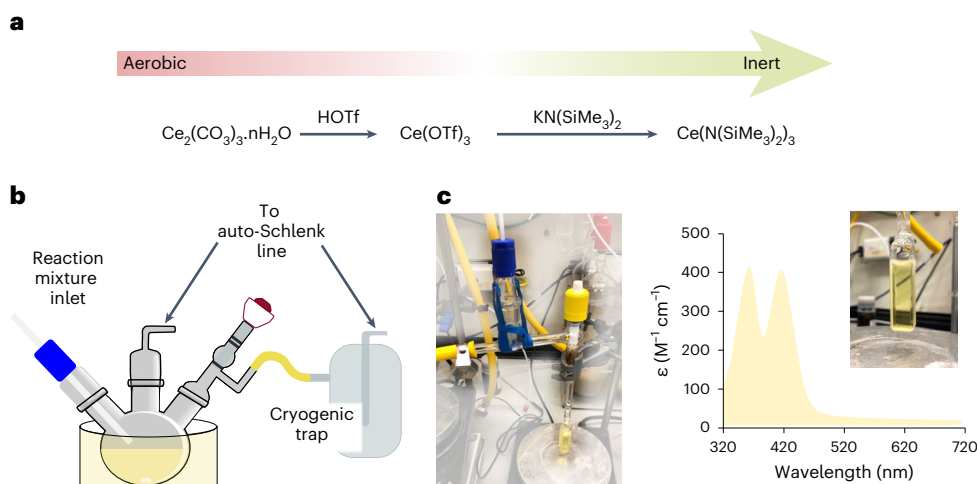
Having designed a programmable hardware and software system for inert-atmosphere synthesis, four sensitive compounds from across the periodic table were chosen to develop the Schlenkputer implementation. For our purposes, a single compound from each block was chosen to demonstrate the versatility of the Schlenkputer: *s* block: [(<sup>o</sup>pp)NacNac)Mg]<sub>2</sub>, *d* block: [Cp<sub>2</sub>Ti<sup>III</sup>(MeCN)<sub>2</sub>]<sub>2</sub>[ZnCl<sub>4</sub>], *p* block: B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub> and *f* block: Ce<sup>III</sup>(N(SiMe<sub>3</sub>)<sub>2</sub>)<sub>3</sub>. Each has a different sensitivity profile, with some sensitive to oxygen and others moisture, as well as temperature and vacuum.

**Titanocene colorimetric oxygen indicator.** All known automated chemical systems exploit LH pumps and valves 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<sub>2</sub>Ti<sup>III</sup>(MeCN)<sub>2</sub>]<sup>+</sup>. The titanocene species [Cp<sub>2</sub>Ti<sup>III</sup>(MeCN)<sub>2</sub>]<sup>+</sup> is one of the most widely used colorimetric indicators<sup>26,27</sup>, 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 the ability to exclude air

from the pump–valve liquid handling system of the Schlenkputer. By transferring the blue solution through the sets of valves and pumps, we could identify trapped air within the system.

We immediately identified the connections between the valves and pumps, as well as the connections between individual valves as being ‘dead’ areas where the Schlenkputer line was unable to purge (Fig. 3a). When transferring the blue titanocene solution between valves, rapid decolorization was observed. To address this, we adopted two complementary approaches that can both be used to inertize liquid handling systems: (1) when inertizing a reactor flask, the liquid handling tubing connecting the glassware and 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. 3a, yellow). (2) Removing air from the connection between valves (Fig. 3a, 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. 3c).

The synthetic protocol for the synthesis of [Cp<sub>2</sub>Ti<sup>III</sup>(MeCN)<sub>2</sub>]<sup>+</sup> (Fig. 3b) involves the suspension of the air-stable bis(cyclopentadienyl) titanium(IV) chloride in acetonitrile, followed by reduction over zinc dust. During the reduction, the red solution turns first green, then deep blue in the absence of air; however, oxygen exposure results in rapid decolorization. To achieve the automated synthesis and isolation of the product, the reaction was setup to involve two RBFs and one crystallization (Schlenk) flask (Fig. 2d). Each RBF was charged with one of the



**Fig. 4 | 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 the removal of solvent using an isolable cryogenic trap. **c**, Automated UV-vis solution sampling allowed for the spectroscopic analysis of the Ce(III) product.

solid reagents. The automated procedure prompts the user to charge the flask at the appropriate time (that is, 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 approximately 15–20 min (Fig. 3e,f). Remote notification steps that 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. This feature also allows the user to adapt the procedure should this be desired in the middle of a run, for example, if a different solvent is required to dissolve an intermediate.

After setup, the  $\text{Cp}_2\text{TiCl}_2$  (8.3 g, 29.7 mmol) is then dissolved in acetonitrile:tetrahydrofuran (THF) (35 ml:75 ml) before the red solution is transferred to the Zn (2.3, 35.2 mmol)-containing flask with stirring for 30 min. 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  $\text{Et}_2\text{O}$  and the flask sealed for 48–72 h, during which time the solution remains deep blue. Finally, the bottom tap on the Schlenk flask is opened to pump out the mother liquor and yield the crystalline product (5.0 g, 43%) on the Schlenk filter frit. These crystals can be isolated for X-ray diffraction (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. 3d).

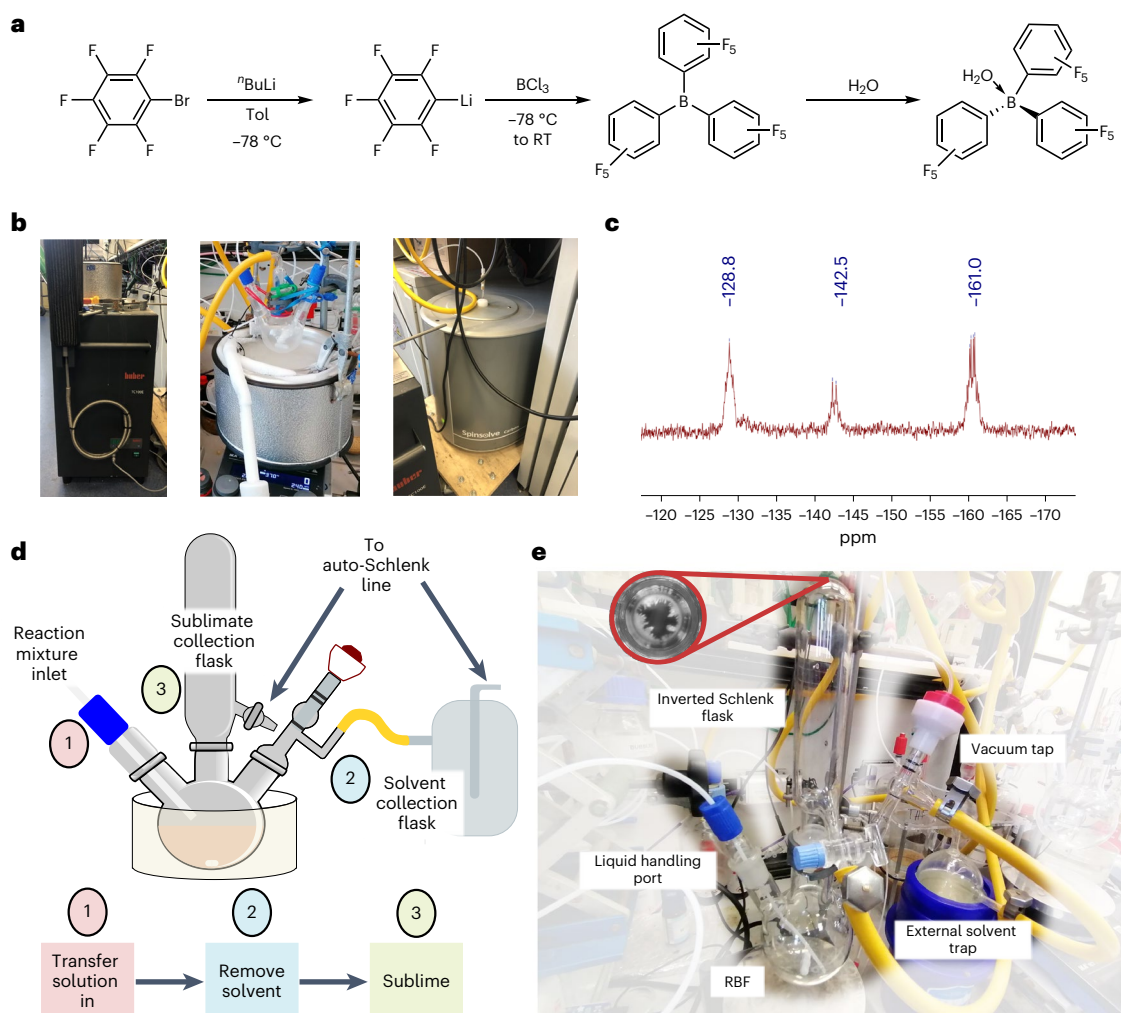
**A highly oxidizable *f* block silylamide.** Lanthanide coordination chemistry is another field that relies upon inert-atmosphere techniques<sup>28,29</sup>. While most lanthanides exist almost exclusively in the 3+ oxidation state, cerium is one of the few that, in addition to undergoing rapid ligand hydrolysis, is readily oxidized in air to Ce(IV) owing to its position within the *4f* block. We next targeted a widely used cerium amide that has been previously shown to exhibit luminescent properties, but that can also act as a precursor for a wide range of novel lanthanide species<sup>30</sup>. For inert and anhydrous chemistry on salts to succeed, it is vital that the precursors reagents are free from water coordination. 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 (for example,  $\text{SOCl}_2$ ,  $\text{TMSCl}$  and  $\text{TF}_2\text{O}$ ) are often highly corrosive and could be detrimental

to the automated systems. Thus, our ability to automate the handling of these compounds was investigated.

Addition of excess neat triflic acid to an aqueous suspension of  $\text{Ce}_2(\text{CO}_3)_2$  was undertaken using the liquid handling backbone of the Schlenkputer under air (Fig. 4a). The resulting acid suspension was first refluxed (100 °C) in an RBF connected through a Findenser 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, infrared spectroscopy demonstrated that the resulting  $\text{CeOTf}_3$  was free of hydration by the absence of the key –OH band at ca.  $1,650\text{ cm}^{-1}$  (cf.  $1,657\text{ cm}^{-1}$  in  $\text{CeOTf}_3 \cdot x\text{H}_2\text{O}$ ; Supplementary Fig. 10)<sup>31</sup>.

Our adapted literature procedure<sup>30</sup> for the synthesis of  $\text{Ce}(\text{N}(\text{SiMe}_3)_2)_3$  consisted of the salt metathesis reaction of anhydrous  $\text{Ce}(\text{OTf})_3$  (0.5 g, 0.867 mmol) with  $\text{KN}(\text{SiMe}_3)_2$  ( $\text{KN}^+$ , 0.54 g, 2.707 mmol) in THF (10 ml), yielding highly soluble  $\text{CeN}^{3+}$  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<sup>2,5</sup>; 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 formation of  $\text{Ce}(\text{N}(\text{SiMe}_3)_2)_3$ , the solvent was removed by connection of the automatically controllable side arm to a cryogenic trap, which was maintained under dynamic vacuum using the Schlenkputer, for 16 h (Fig. 4b). 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  $\text{Ce}(\text{N}(\text{SiMe}_3)_2)_3$  (0.187 mg, 37%, compound 2).

Since this cerium complex also exhibits a characteristic yellow color indicative of the Ce(III) oxidation state, the product has been characterized 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 that allowed facile connection to both the liquid and gas handling systems of our Schlenkputer, while also being sealable for transport to the relevant spectrometer (Fig. 4c). UV-vis analysis of the yellow solution was in



**Fig. 5 | Synthesis and isolation of BCF, a highly hygroscopic Lewis acid.**  
**a**, Reaction scheme for the synthesis of  $B(C_6F_5)_3$ . Tol, PhMe. **b**, Incorporation of an ultra-low-temperature chiller unit allowed for automated reactivity at temperatures as low as  $-100\text{ }^\circ\text{C}$ . **c**, Inline low-field NMR analysis can detect the

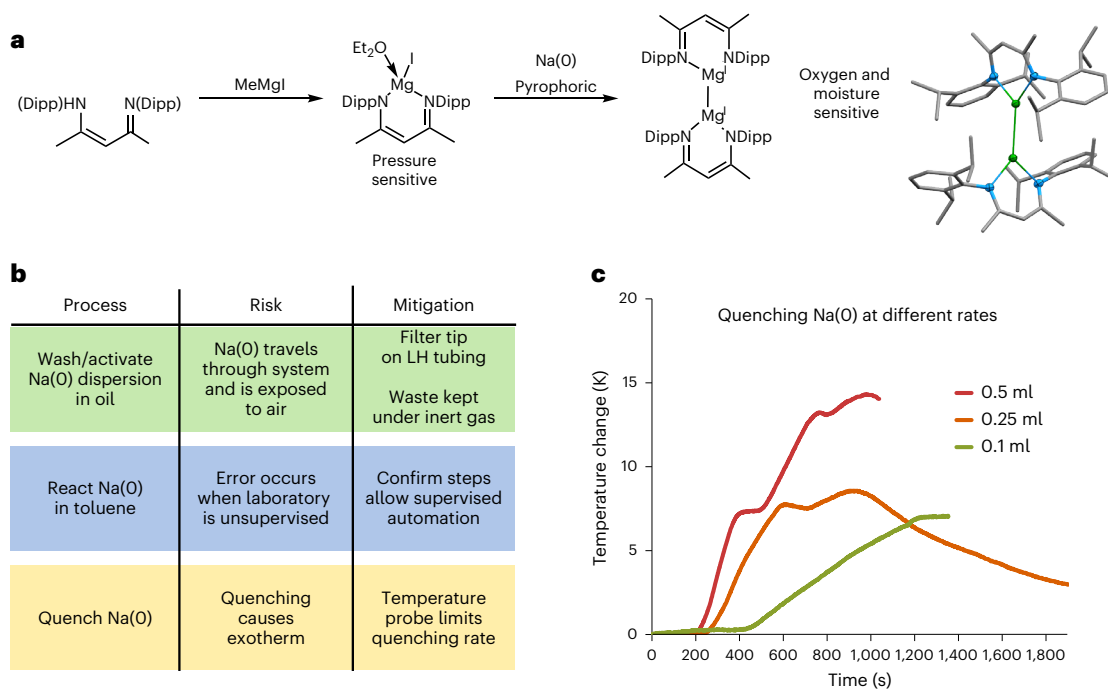
formation of the desired product with no evidence of hydration. **d**, A schematic showing the setup and function of the automated evaporation and sublimation apparatus. **e**, A photograph of the setup and glassware used for automated sublimation of  $B(C_6F_5)_3$ .

keeping with published spectra<sup>30</sup>. Subsequent exposure of the sample to air for a brief period (ca. 3 s) resulted in immediate darkening of the solution to deep orange/brown (Supplementary Fig. 12). NMR sampling was also developed and explored for both  $CeOTf_3$  and  $CeN^+$ . 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.

**Accessing the hygroscopic Lewis acid BCF.** Tris(pentafluorophenyl) borane (BCF) is a highly moisture-sensitive Lewis acid<sup>32</sup>. Accessed through the formation of an aryllithium intermediate, BCF, like many other highly reactive species, is synthesized at very low temperatures ( $<-70\text{ }^\circ\text{C}$ ). In addition, the final product is often purified by double sublimation or sublimation followed by crystallization, a process that has not previously been automated. This borane has several NMR handles that 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 three- and four-coordinate examples (Fig. 5a). To achieve this synthesis in an automated fashion, we therefore required the incorporation of an automated chilling system that was

able to reach temperatures as low as  $-90\text{ }^\circ\text{C}$ , 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 reaction progress. 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 minimize the requirement for bespoke equipment. Lithiation and coupling were carried out in a single flask which was cooled to  $-80\text{ }^\circ\text{C}$  automatically (Fig. 5b) before the temperature was autonomously raised to ambient over  $\sim 120$  min. A portion of the reaction mixture was then transferred to the appended flow NMR cell and subject to  $^{19}\text{F}$  NMR, which demonstrated formation of the desired product (Fig. 5c)<sup>33–35</sup>.

Pure BCF is most commonly obtained through inert-atmosphere sublimation to separate the product from LiCl and other impurities<sup>36</sup>. For manual sublimation, it is common to charge a sublimation tube with a solid crude product that can then be heated under vacuum and condensed on either a second room temperature (RT) tube or on a cold finger. To eliminate this manual step, we transferred the product solution into a flask and removed the solvent *in situ*. The reaction mixture was thus transferred into a three-necked RBF appended with an external cryogenic trap for automated solvent removal (Fig. 5d,e). As for  $CeN^+$  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.



**Fig. 6 | Alkali metal reduction to generate Mg(I).** **a**, Reduction of (NacNac)Mg<sup>I</sup> with Na(O). **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(O) with *i*PrOH (15% in toluene). Monitoring stopped upon observation of no further temperature increase.

**Alkali metal reduction to Mg(I).** Accessing unusual 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<sup>37–39</sup>. However, their use in organic solvents can present hazards, which makes their automation challenging and a high level of expertise is required for their manual handling.

We next undertook an alkali metal reduction reaction to yield Stasch and Jones' Mg(I) dimer<sup>40</sup> utilizing the Schlenkputer system (Fig. 6a), providing a safe method for reacting with and quenching Na(O) 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 these 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(O) handling. The first step in the magnesium reduction requires the metalation of the <sup>Dipp</sup>NacNac ligand (L) to yield moisture- and vacuum-sensitive LMgI(OEt<sub>2</sub>)<sub>n</sub> (Fig. 6a).

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(O) in oil before cycling of the entire system. This dispersion exhibits markedly lower sensitivity to air, such that handling by non-experts 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 that was maintained under a stream of N<sub>2</sub> for safety (Fig. 6b). 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 a stoichiometric reaction. The solution of LMgI(OEt<sub>2</sub>)<sub>n</sub> was transferred onto a suspension of Na(O) in toluene and the mixture stirred overnight. The solution was then automatically filtered and extracted into hexane to yield the product dimer [(<sup>Dipp</sup>NacNac)Mg]<sub>2</sub> (0.328 mg, 43%), 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. To determine the safest addition rate, we carried out the Na(O) quenching at various aliquot addition volumes and monitored the resulting solution temperature (Fig. 6c). 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.

## Discussion

The automation of highly sensitive inert-atmosphere syntheses has been demonstrated. We have described how to design an automatable and remotely operable gas/vacuum handling manifold, the Schlenkputer, that can reduce system oxygen and water levels below 1 ppm, and demonstrate how to integrate this with a liquid handling robotic platform. We have designed a basic set of glassware that can be utilized alongside classical Quickfit glassware to undertake highly reactive synthesis. In demonstration of the abilities of our system, we have synthesized four highly sensitive exemplar compounds from across the periodic table: Cp<sub>2</sub>Ti<sup>III</sup>(MeCN)<sub>2</sub> (**1**), Ce<sup>III</sup>{N(SiMe<sub>3</sub>)<sub>2</sub>}<sub>3</sub> (**2**), B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub> (**3**) and {<sup>Dipp</sup>NacNacMg<sup>I</sup>}<sub>2</sub> (**4**), each with different synthetic challenges and sensitivity profiles. In this manner, we have demonstrated inert-atmosphere synthesis, crystallization, solvent distillation/evaporation and sublimation, as well as analytical sampling, inline analysis, low-temperature reactivity and handling of pyrophoric alkali metals.

Combined, this platform provides a highly reconfigurable reactor system for the small- to medium-scale (0.1–100 g) batch synthesis and isolation of air-, moisture- and temperature-sensitive compounds, complementing alternative strategies and technologies for working with sensitive materials such as placing automated reactors inside a glovebox, which has been undertaken by companies such as ChemSpeed and LabUnlimited. As such, the Schlenkputer system fills the gap between

high-throughput reaction discovery (in a glovebox) and industrial-scale processes (with remote control or automation), allowing for bench-scale reaction development, optimization and robust, safe reproduction. The Schlenkputer provides a flexible, low-throughput platform to address processes that may be undesirable to undertake inside a glovebox, for example, experiments with reactive gases (such as H<sub>2</sub>), at very low temperatures, or for anoxic aqueous reactions, and provides an adaptable alternative for experiments that could also be conducted inside a glovebox, such as inline analysis (for example, off-gas analysis), kinetics measurements (for example, for polymerization), convergent organometallic syntheses (for example, Grignards) or parallel reactions (for example, Design of Experiments). Thus, this work demonstrates a comprehensive system for automation of inert-atmosphere manipulations, potentially dramatically increasing the safety and efficiency of handling highly reactive chemical species.

## Methods

### General experimental methods

All reactions were carried out under inert atmosphere using the technology described herein to evacuate and refill glassware with N<sub>2</sub> gas cylinder purging throughout the reaction. Unless otherwise stated, isolated sensitive materials were stored and prepared for offline NMR and XRD analysis in a nitrogen-atmosphere MBraun Labstar glovebox with O<sub>2</sub> levels <1 ppm and H<sub>2</sub>O levels <2 ppm. Solvents (excepting hexane) were obtained from a solvent purification system and dried over activated 3 Å molecular sieves for 48 h after collection. Anhydrous hexane solvent was purchased from Sigma-Aldrich and stored over activated 3 Å molecular sieves under nitrogen. Deuterated solvents for NMR analysis were dried over activated 3 Å molecular sieves. NaCac<sup>Dipp</sup> ligand was prepared manually by a published method<sup>1</sup>. Anhydrous cerium triflate for the synthesis of Ce(N{SiMe<sub>3</sub>}<sub>2</sub>)<sub>3</sub> was kindly provided by Tajrian Chowdhury from the group of Dr Joy Farnaby and prepared manually by their method, before our automated synthesis of CeOTf<sub>3</sub> 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 Bruker Avance III HD 600 MHz or Bruker Avance II 400 MHz spectrometers. Chemical shifts ( $\delta$ ) are reported in parts per million (ppm) downfield from tetramethylsilane and, for offline samples, are referenced to residual protium in the NMR solvent (C<sub>6</sub>D<sub>6</sub>,  $\delta$  = 7.16 and THF-d<sub>3</sub>,  $\delta$  = 3.58). X-ray crystal structures of compounds **1** and **4** were collected on a Bruker Apex-II diffractometer and confirmed to match entries 1167669 (**1**) and 661566 (**4**) in the Cambridge Structural Database. Chilling was provided by a Huber TC100E cooling system.

### Synthesis of [Cp<sub>2</sub>Ti(CH<sub>3</sub>CN)<sub>2</sub>]<sub>2</sub>[ZnCl<sub>4</sub>] (**1**)

Using the Schlenkputer system and following an adapted literature procedure<sup>2</sup>, 8.3 g (29.7 mmol, 1 eq.) of Cp<sub>2</sub>TiCl<sub>2</sub> 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 min. 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 48 h leading to the precipitation of compound **1** as dark-blue crystals (5 g, >43%, 6 runs). To extract crystals for XRD, Fomblin Y Oil was added to the flask to allow their handling in air. Screening experiments determined the unit cell parameters to be  $a = 28.4$ ,  $b = 15.2$  and  $c = 15.4$  Å for an Orthorhombic cell with  $V = 6,648$  Å<sup>3</sup> matching Cambridge Structural Database entry 1167669 (ref. 2).

### Synthesis of Ce(N{SiMe<sub>3</sub>}<sub>2</sub>)<sub>3</sub> (**2**)

Using the Schlenkputer system and following an adapted literature procedure<sup>3</sup>, the white powders Ce(OTf)<sub>3</sub> (0.5 g, 0.867 mmol, 1.0 eq.)

and KN(SiMe<sub>3</sub>)<sub>2</sub> (KN', 540 mg, 2.707 mmol, 3.1 eq.) were weighed into a J Young tapped ampoule in the glovebox. THF (10 ml) was added to suspend the reagents, and a slow color change from colorless to pale yellow was observed. The mixture was stirred at RT for 2 h 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 × 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'<sub>3</sub> (187 mg, 35%).

### Synthesis of B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub> (**3**)

Using the Schlenkputer system and following an adapted literature procedure<sup>6</sup>, to a stirred solution of bromopentafluorobenzene C<sub>6</sub>F<sub>5</sub>Br (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 min, followed by further addition of toluene (5 ml) to ensure complete washing of the *n*-BuLi from the liquid-handling tubing. The resulting colorless suspension was stirred for 1 h at this temperature. A boron trichloride/*n*-hexane solution (4.2 ml, 1 M, 4.2 mmol) was then added within 50 s before further washing of the liquid-handling tubing with toluene (5 ml), and the resulting colorless suspension was then slowly warmed to ambient temperature over a period of 90 min. In situ <sup>19</sup>F NMR analysis was conducted by transferring 10 ml of the reaction mixture to the NMR machine's flow cell to confirm conversion (note: this contrasts with the time reported in the literature procedure we based our work on<sup>6</sup> and demonstrates the value of inline analysis using automation for optimizing chemical synthesis). The whole solution was then transferred through a frit to a three-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 (Supplementary Figs. 7 and 22). 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<sub>6</sub>F<sub>5</sub>)<sub>3</sub> (840 mg, 38%, three runs) as a colorless, needle-like solid.

### Synthesis of [(<sup>Dipp</sup>Nacnac)Mg]<sub>2</sub> (**4**)

Starting material <sup>Dipp</sup>NacnacH was prepared according to a method reported in the literature<sup>8</sup>. Under nitrogen, MeMgI (0.68 ml, 3.0 M in Et<sub>2</sub>O, 2.05 mmol) was added to a stirred solution of <sup>Dipp</sup>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 {<sup>Dipp</sup>NacnacMg}(OEt<sub>2</sub>)} solution was allowed to reach RT, yielding a colorless precipitate. Meanwhile a separate three-neck round-bottom flask, appended with a temperature probe, was charged with a sodium in oil dispersion (ca. 9 ml, 40% wt/wt Na(0)) and washed with hexane (3 × 20 ml) with stirring, before the 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 that was redissolved in hexane, filtered and the solvent removed under reduced pressure to give [(<sup>Dipp</sup>Nacnac)Mg]<sub>2</sub> (328 mg, 43%, five runs) 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. 6c. NMR data were consistent with literature values for compound **4** (ref. 9).

## Data availability

The article and Supplementary Information include all data and materials required to reproduce this work. This includes .xdl and .json files for each synthesis and full analytical data as well as details on and photographs of the bespoke hardware described herein to allow reproduction. Supplementary videos show examples of the procedures underway in the Schlenkputer system. This is all available on Zenodo



at <https://doi.org/10.5281/zenodo.10327909>. Source data are provided with this paper.

## Code availability

The code is available via the Zenodo repository at <https://doi.org/10.5281/zenodo.10327909>.

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### Author contributions

The concept was conceived by L.C., who also managed the team, raised the funding and designed the programming language. N.L.B. and L.C. designed the programmable manifold, and N.L.B. devised the experiments. Laboratory work and data analysis were carried out by N.L.B., F.B., A.B. and D.R.W. Integration of the low-temperature chiller was achieved by V.S.L. The paper and associated materials were prepared by N.L.B. with help from L.C.

### Competing interests

Some of this work has been filed as a patent by the University of Glasgow, number 2307382.8 (status, pending).

### Additional information

**Supplementary information** The online version contains supplementary material available at <https://doi.org/10.1038/s44286-023-00024-y>.

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