When I started thinking about a PhD, I knew I wanted to work in a field that crossed boundaries but still used the organic synthesis I had learned in my master’s project. When I read Dave Leigh’s paper on the construction of an artificial molecular synthesizer that mimics the ribosome, I knew straightaway that building artificial molecular machines would fit the bill!1 When I visited Manchester, I loved the creative and collaborative approach of the Leigh group and signed up. During my PhD, I worked on a range of different machines, including a system of rotary and linear molecular machines powered by pulses of a chemical fuel2 and a new kind of artificial molecular synthesizer, published in this issue of Chem,3 among other projects.4,5

On my first day in the laboratory in Manchester, I met with Dave and Dr. Guillaume De Bo, then a postdoc in the group, to discuss my PhD project. They suggested that I try to extend the molecular synthesizer concept to reactions that the ribosome cannot perform, in particular to look at the Wittig reaction. The project fitted perfectly with my interest in molecular machines and organic synthesis, so I dived in with relish while thinking, “How hard could it be?” As a brand-new PhD student, I perhaps did not quite appreciate the amount of synthesis, or number of redesigns, that would be needed in the coming years! Still, with excitement and a modeling kit, I embarked on the synthesis of my first artificial molecular machine.

The Leigh group’s artificial molecular synthesizers are based on mechanically bonded rotaxane architectures, that is, rings wrapped around linear axles. Mechanical bonds are ubiquitous in artificial molecular machines because they allow us to orchestrate the relative motion of different parts of a machine: constraining motion in certain directions while allowing it in others. Leigh’s artificial molecular synthesizers work by guiding the ring along the linear axle of the rotaxane such that the ring picks up sequence information in the form of barriers as it goes along. To design a new synthesizer that used the Wittig reaction to form carbon–carbon double bonds, we needed to find ways to embed the required phosphonium salts into the track of our rotaxane. Because these molecular synthesizers are complex and require multiple synthetic steps, we also had to understand which reactions would be tolerated by phosphonium salts. I found out early on that what looks good on paper does not always transfer to the flask. I originally intended to use palladium-catalyzed coupling reactions to link together phosphonium salts in a rigid track. Unfortunately, all the coupling conditions I tried led to decomposition of the phosphonium salt. This underlined the advantage of designing molecular machines from scratch—we could simply alter the design to use different chemistry and so avoid this problem. I chose to use triazole linkages, whose formation was well tolerated by phosphonium salts.

Future generations of this molecular synthesizer concept used only triazole linkages to build up large assemblies. This allowed me to form my targeted molecules, only to uncover a new problem: when I tried to activate the machines, nothing seemed to happen. Mass spectrometry—the simplest way to analyze such complex structures—showed no change in mass upon the addition of a strong base but did show
a second peak, an adduct with sodium. This made little sense initially given that the original phosphonium salt was positively charged. On reflection, I realized that this showed a key problem with my design: the machine had fully reacted and so had become a neutral species, but the macrocycle was unable to fall off the track after reaction because it was trapped by the phosphine oxide. My barrier units were simply too large!

As is often the case with molecular machines, modeling is of limited efficacy, and the only way to find the perfect size, shape, and conformation of subcomponents is, as in drug discovery, by well-informed trial and error. By tweaking the size of my macrocycle and barrier units, I was ultimately able to find a balance between stability before operation and ease of de-threading after reaction.

A working molecular machine was now in sight—my designs were able to pick up a single barrier unit and attach it to the macrocycle but struggled to synthesize longer tracks as a result of the instability of the barrier units I was using. As so often happens in research, the inspiration for the solution came from a tangential source. When searching for a chemical I needed for another project, I noticed a dialdehyde where the conjugation between the two aldehydes was broken by an sp³ linker. I realized that the instability I was seeing in my synthesizer might come from the conjugation of the phosphonium ylide formed under operation conditions and the aldehyde of the same barrier. To test this hypothesis, I designed a new barrier unit with conjugation between the phosphonium ylide and aldehyde broken by an sp³ carbon. Three years into my PhD, this was my final roll of the dice for this machine—either it worked now, at the eighth design, or I would have to move on.

Thankfully, the eighth time’s a charm—I was able to make a rotaxane that could pick up a sequence of four barrier units, in a specific and specified sequence, and print them onto the end of a growing chain (Figure 1).³ Our machine is able to perform sequence-specific synthesis inspired by the ribosome but using chemistry that the ribosome cannot, given that the ribosome is constrained by the operating conditions of the cell. As such, our machine can autonomously perform a task that biological machines cannot, underlining the advantages of constructing molecular synthesizers from scratch.
After my PhD, I moved to the University of Cambridge to work with Prof. Jona-
than Nitschke on self-assembled molecu-
lar capsules, most recently as a Lever-
hulme Early Career Research Fellow and a Research Fellow at Sidney Sussex Col-
lege, Cambridge. After the lengthy (up to 50 steps per machine!) synthesis of
my PhD, I thought it could be useful to
learn how to program molecules to
form complex architectures by them-
selves! In the future, I hope to start my
own research group applying artificial
molecular machines and molecular cap-
sules inspired by my PhD and postdoc-
toral research to challenges in biomed-
ical science. A key goal will be to
minimize my students’ design iterations!

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