
On the Right “Track” to Artificial Assemblers

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The design of synthetic analogs to biological molecular machines offers a new vista for chemists. In this issue of Chem, McTernan et al. report an artificial synthesizer reminiscent of natural assemblers. This molecular machine is capable of forming sequence-defined oligomers by the Wittig reaction, a transformation not found in nature.

In living organisms, countless molecular machines perform myriad tasks simultaneously, from ATPases producing adenosine triphosphate to the motor proteins responsible for the transport of cellular cargo. One of the most famous and well-studied biological machine is the ribosome. Essential for the synthesis of proteins, the ribosome uses the codons of a messenger RNA (mRNA) strand as a “barcode” to sequentially add amino acid monomers to a nascent peptide. The mechanism by which the ribosome synthesizes various proteins has been investigated in great detail and is quite remarkable in that it is sequence specific. Each codon, consisting of three DNA bases, encodes the introduction of a specific amino acid into the growing chain. This peptide elongation is immediately followed by a shifting of the mRNA strand, exposing the next codon to the ribosome. Thus, the ribosome can be seen as a kind of molecular walker because it moves stepwise along the mRNA track used for protein synthesis in the translation step.

Biological machines are extremely efficient, yet this comes at the cost of high complexity and heavy specialization. This is one of the reasons chemists have been trying to develop simplified synthetic molecular machines for decades. By trying to mimic mother nature, simpler and smaller molecular machines have been capable of similar exploits.1 To this date, we cannot compete with nature’s efficiency, yet the toolbox of reactions, reagents, and stimuli available to the synthetic chemist is almost limitless in comparison to the biologically relevant environment.2 Fundamental operations such as substrate transport, artificial muscle actuation, or stepwise motion3,4 using artificial and biohybrid machines have been achieved. In order to move forward, the field must now focus on two different challenges: bridge the gap between artificial and biological molecular machines and extend the scope of what nature can do.

In this issue of Chem, McTernan et al. report the design of an artificial machine that can synthesize all-carbon oligomers by consecutive Wittig olefinations.5 The machine’s backbone is based on a rotaxane skeleton. Rotaxanes are mechanically interlocked molecules composed of two subunits: a macrocycle and a rod. By careful design of the steric bulk of the end groups of the rod, a macrocycle can be threaded and trapped on the elongated track. Despite the absence of covalent bond—and, in some cases, of any non-covalent attractive interactions—between the macrocycle and the thread, the two subunits are joined by what is termed a mechanical bond.6 An interesting property arising from this peculiar interaction is that the position, movement, and local environment of the macrocycle can be controlled by designing suitable interactions.

The structure of rotaxanes can somewhat be viewed as a stepwise assembling machine. Indeed, although the threading of the macrocycle yields defined molecular assemblies, the back-and-forth shuttling by relative

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motion of the subcomponents make ro-
taxanes molecular walkers. In fact, the
Leigh group previously reported a ro-
taxane-based molecular machine that
mimics the role of the ribosome. By
installing a cysteine pendant arm on
the macrocycle of a rotaxane as well as
amino acid stations on the rod, the
authors demonstrated the stepwise
incorporation of up to four amino acid
monomers into a short peptide. In
their work described in this issue of
Chem, McTernan et al. now expand
the scope of the artificial synthesizer
to perform a C=C bond formation
step via a Wittig reaction, otherwise un-
heard of in nature.

Their design is schematically repre-
sented in Figure 1. The macrocycle is
minimally functionalized, incorporating
a pyridine group for ease of synthesis
(see below) and a reactive aldehyde
group. On the rod, multiple phosphin-
ium ylide stations bearing 2,2-diaryl-
propane groups act as both a mono-
mer transfer agent as well as a
physical barrier to prevent random
shuttling of the macrocycle along the
thread. These reactive stations are con-
ected through a rigid array of aryl rings
to prevent folding of the track. This
track is terminated at one end by a
bulky stopper to prevent dethreading
of the macrocycle, and the other end
is left open for release of the product.

The rotaxane is first constructed by us-
ning an active metal template strategy.
By copper-catalyzed azide-alkyne
cycloaddition, the rod’s stopper and
the first phosphonium station are
clicked together by a triazole group.
This is where the pyridine-function-
ized macrocycle comes in handy, given
that the incorporation of a copper-
coordinating moiety in the ring allows
this cycloaddition to be performed
across the ring, effectively threading
the rotaxane in one step. Iterative cy-
cloadditions were then used to elon-
gate the track to up to four stations
bearing different monomers.

Upon treatment of the rotaxane with a
resin-bound superbase, formation of
phosphonium ylides on the rod triggers
consecutive Wittig reactions with the
elongating macrocycle’s aldehyde. The
formation of a C=C bond on the macro-
cycle specifically incorporates the mono-
mer of the closest phosphonium ylide sta-
tion, transforming the latter into the
 corresponding phosphine oxide. Conve-
niently, the reduced size of the phos-
phine oxide now allows shuttling of the
macrocycle to the next station, where
the subsequent monomer can be intro-
duced. By iterative addition of the 2,2-di-
arylpropane groups onto the macrocycle,
the oligomer is elongated until the last
monomer is incorporated and the macro-
cycle can slide off the thread.

Figure 1. The Artificial Assembler Sequentially Adds Carbon-Based Monomers to an Elongating
Oligomer
After the successive Wittig reactions and dethreading of the ring, an oligomer exclusively based on a carbon–carbon bond backbone is obtained. From this new design, compounds that could not be obtained with a biological machine were isolated. Each station was functionalized with differently substituted 2,2-diarylpropane monomers. Arguably, these substituents should not have a great effect on the reactivity of the corresponding phosphinium ylide, and thus would yield a statistical mixture of products should this reaction be performed in solution. But the very way this synthesizer works, namely by iterative addition of spatially separated monomers, allows the sequence-specific introduction of these structurally similar monomers. Furthermore, although the E/Z selectivity of each Wittig reaction should be improved, the authors calculated that an all-Z product isomer would adopt a helical conformation. The secondary structure of peptides is intrinsically linked to their biological properties and is therefore of prime importance. What the authors thus demonstrated is that an artificial machine can de novo synthesize artificial products that might share resemblance in their secondary structure to natural compounds.

Undoubtedly, there is still a long way to go before an artificial synthesizer can be applied for the efficient synthesis of complex structures. Many key points are raised by the authors for the field to develop further. Among them, one major challenge to overcome is the reusability of the whole synthesizer. Re-functionalization strategies are necessary in order to reset the synthetic machine. The difference in activity compared with that of their biological counterpart is also important. Although the ribosome can assemble multiple amino acids per second, this artificial machine requires up to 5 days to make 4 bonds. Reading and translating information in the assembly process is also a major challenge. But the game is worth the candle. Biological synthesizers are limited in their substrate scope. The ribosome can assemble polyamides, DNA polymerases can stitch nucleosides together, but the myriad reactions available to the synthetic chemist renders limitless the applications of artificial synthesizers.

In this paper, Leigh and colleagues report the design, synthesis, and performances of an artificial molecular machine synthesizing unnatural substrates by performing reactions that are absent in the biological world. By taking inspiration from biological assemblers, the authors blur the lines between artificial and natural molecular machines and bring a new twist to the biomimicry approach.

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