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Catalytic length-controlled oligomerization with synthetic programmable templates

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Bartosz M. Lewandowski, Dario Schmid, Rüdiger Borrmann, Dominik Zetschok, Martin Schnurr & Helma Wennemers

Nature uses templated length-controlled oligomerization to process genetic information. Templates that are DNA and RNA based and fully synthetic have also been developed for preparing unnatural oligomers. However, these reactions require stoichiometric amounts of the template for product formation. Here we report a catalytic macrocyclic template that promotes the oligomerization of a small-molecule substrate with a remarkable degree of length control. The design of the template is based on rigid oligoproline moieties decorated with catalytic sites in a defined spatial arrangement. The dimension of the macrocycle and the number of catalytic moieties determine the number of monomers that are incorporated into the growing oligomer, thus allowing access to specific products with lengths preprogrammed by the template.

Templated synthesis is key to the production of natural oligomers from the respective monomeric building blocks[1]. For example, the genetic information is transcribed from DNA into RNA and then translated into peptides and proteins. The natural DNA-based oligomerization machinery has been manipulated by scientists such that it allows for the synthesis of any desired complementary DNA and RNA strand[2–4]. This approach has even been used for the synthesis of sequence-controlled non-natural oligomers (Fig. 1a)[5–10]. Impressive progress has also been made in templated oligomer synthesis with non-DNA-based templates[11] and has enabled access to macrocycles[12] and cages[13] from monomeric non-natural building blocks. Furthermore, dynamic covalent chemistry tools have facilitated the creation of self-replicating macrocycles[14–16]. These are formidable achievements because even the controlled formation of macrocycles from a single precursor is still challenging[17]. Templating also allowed for the synthesis of linear oligomers with length control, which is particularly difficult because they bear at least one reactive terminus[18–21]. The preparation of such synthetic oligomers with a defined length requires otherwise controlled polymerization conditions[22,23] or successive couplings of the monomers with experimental interventions at each step[24,25]. The templated formation of synthetic oligomers in one pot is therefore an intriguing and enabling alternative to access non-natural oligomers.

An intrinsic limitation of DNA-based templates and all other scaffolds used so far is the tight binding between the template and the complementary strand. The newly formed oligomer is therefore only accessible in stoichiometric amounts relative to the template, and the complex between the template and the synthetic oligomer needs to be disassembled in a subsequent release step[26]. Catalytic turnover has remained elusive in templated oligomerization. Here we report catalytic oligomerization that uses a synthetic template to bind, activate and covalently link monomeric building blocks in one pot with control over the length of the newly formed oligomer.

Results and discussion

We envisioned the following components and features as key to facilitating a catalytic length-controlled oligomerization (Fig. 1b): (1) a macrocyclic template (**T**) decorated with two sets of catalytic sites (green and dark blue) located in defined mutual distances on opposite faces of the cavity; (2) a bifunctional monomeric building block (**M**) bearing two functional groups (blue and light green) that only react with each other upon activation by the catalytic sites of the template; and (3) the formation of an oligomer (**O**) that has a lower binding affinity than the monomeric building blocks to the template. Variations of the length of the template, and thereby the number of bifunctional catalytic sites, should then activate a different number of monomers and lead to the formation of an oligomer with control over its length.

Based on the above considerations, the macrocyclic template must be rigid and built from modular components that allow for facile

Laboratory of Organic Chemistry, D-CHAB, ETH Zurich, Zurich, Switzerland. e-mail: Bartosz.Lewandowski@org.chem.ethz.ch; Helma.Wennemers@org.chem.ethz.ch

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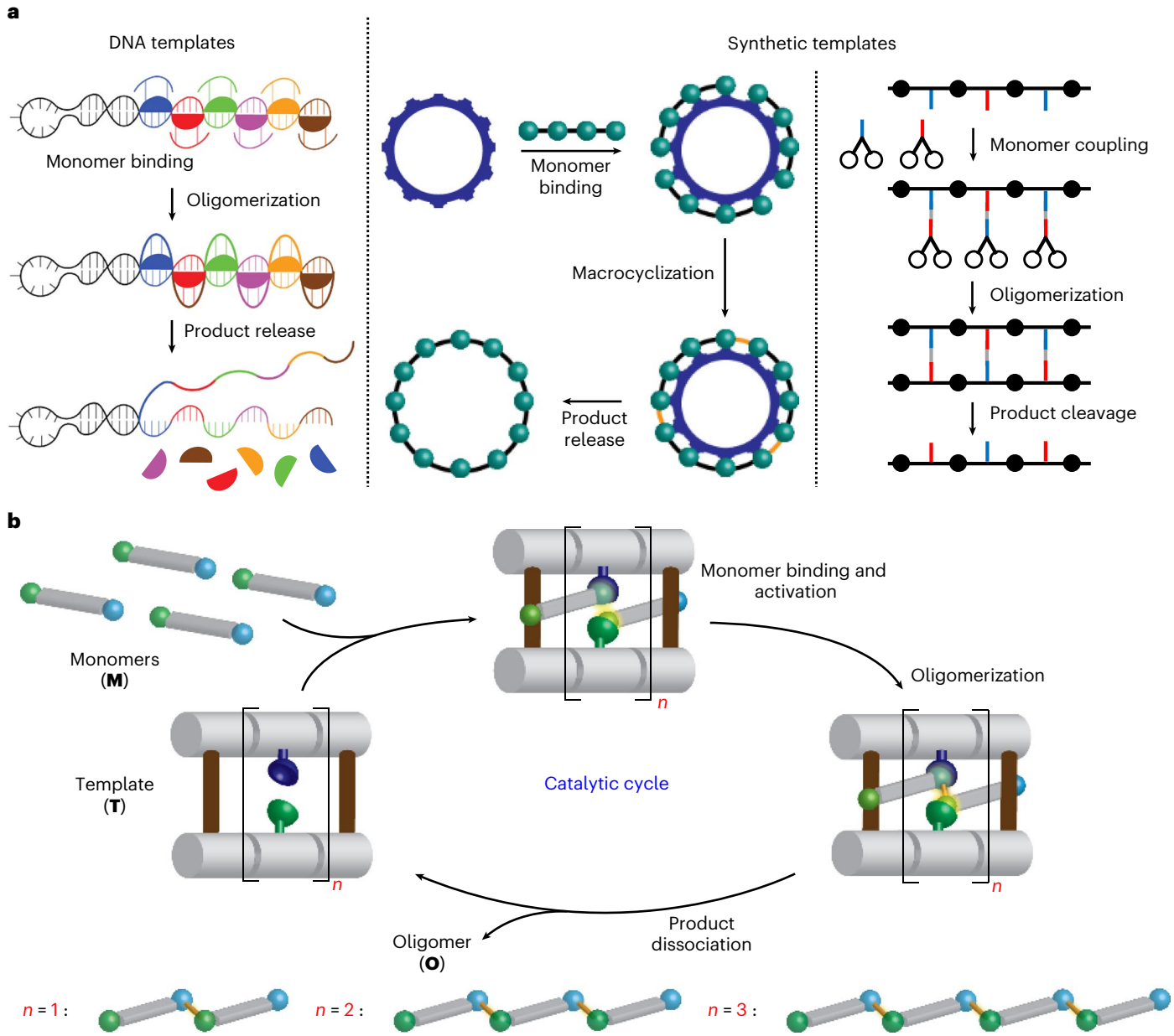

Fig. 1 | Templated oligomerization. a, Stoichiometric examples with engineered DNA templates (left) and synthetic templates (middle and right) of the formation of cyclic and linear oligomers[9,12,20]. **b**, Concept of a catalytic, length-controlled oligomerization with a macrocyclic template.

length variations. Further, the template needs to allow for functionalization with catalytic sites at geometrically well-defined positions. We envisioned that oligoproline-based macrocycles would fulfill all of these requirements (Fig. 2a). Already at a chain length of six residues, oligoprolines form the polyproline II (PPII) helix in which every third residue is located at the same face of the helix at a distance of ~9 Å (Fig. 2b)[27,28]. Thus, the catalytic sites can be aligned on the same side of the helical scaffold to point into the cavity. Further, these peptides can be easily prepared with different lengths by standard solid-phase peptide synthesis (SPPS), are soluble in aqueous and organic solvents and can be derivatized if γ-azidoproline residues are used as building blocks[28].

Macrocycle formation should be possible by connecting two oligoproline moieties, for example, by acyl hydrazone formation, which is a reaction that occurs under mild conditions and is compatible with many other functional groups.

We chose the reaction between a malonic acid half thioester (MAHT) and an aldehyde to explore the length-controlled oligomerization with a macrocyclic template (Fig. 2c). This aldol-type reaction is closely related to the process nature uses for the enzymatic synthesis of polyketides[29]. The MAHT serves as a thioester enolate surrogate and the release of CO_2 is a driving force. Bifunctional organocatalysts with thiourea and amine moieties[30] catalyse this reaction and yield β-hydroxy thioesters via C–C bond formation, followed by decarboxylation[31–33]. We therefore anticipated that macrocyclic templates with thiourea and amine moieties at opposite sides of the cavity should facilitate the length-controlled oligomerization of monomer **1** that bears both an aldehyde and an MAHT group (Fig. 2a,d). The distance between these two moieties in **1** should suffice to span the distance between the two sides of the macrocyclic template. Further, the product β-hydroxythioester, which lacks a carboxylic acid group and thus a coordinating site, should bind significantly less tightly to the thiourea moieties of the template compared to the substrates, and thus dissociate from the catalyst and allow for turnover in the templated oligomerization reaction (Fig. 1b and Fig. 2c,d).

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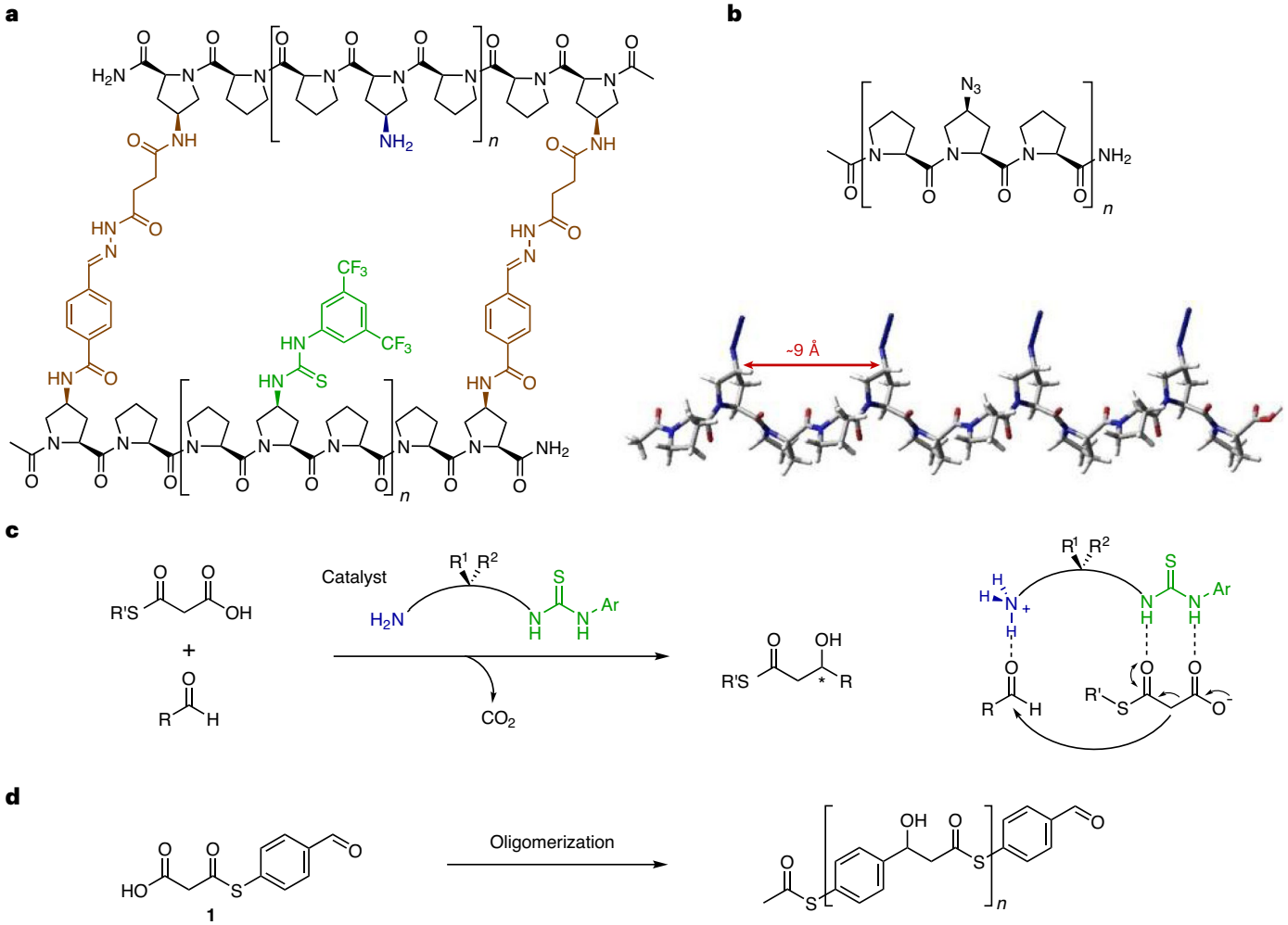

Fig. 2 | Design of the catalytic oligomerization template. a, Structure of the envisioned macrocycles for templated catalysis with catalytic sites in blue and green, and hydrazone linkage in brown. **b**, General structure of oligoprolines with azidoproline residues in every third position (top) and model of a PPII-helical 12-mer (bottom). **c**, Bioinspired decarboxylative aldol-type reaction catalysed by bifunctional catalysts bearing thiourea and amine moieties (left) and plausible activation mode (right). Note that activation is also possible by iminium ion formation and reverse coordination of substrates to the catalytic sites. **d**, Bifunctional substrate for templated oligomerization.

We started our experiments by exploring the synthesis of templates **T1**–**T3** (Fig. 3a). These macrocycles consist of 7-, 10- and 13-mer oligoproline half-macrocycles and contain one, two and three amine-thiourea catalytic pairs, respectively. Thus, **T1**–**T3** were expected to yield the dimer, trimer and tetramer of monomer **1**, respectively, in the templated oligomerization. For the synthesis of the oligoproline building blocks with amine (**H1**–**H3**) and thiourea (**H1'**–**H3'**) moieties, we used proline, (4*S*)-azidoproline and *tert*-butoxycarbonyl (Boc)-protected (4*S*)-aminoproline residues to enable orthogonal functionalization. Their SPPS proceeded seamlessly, including the on-resin installation of the amine and thiourea moieties that were achieved by azide reduction followed by reaction with 3,5-bis-trifluoromethylphenyl isothiocyanate (Supplementary Figs. 1 and 2).

We installed acyl hydrazine and aromatic aldehyde moieties at the terminal proline residues of **H1**–**H3** and **H1'**–**H3'**, respectively, as sites for the macrocyclization. For the macrocyclization, the two half-macrocycles were reacted in a 1:1 ratio in methanol containing 1% of trifluoroacetic acid (TFA) at a dilution of 2 mM (Fig. 3b). Notably, the macrocyclic templates **T1**–**T3** formed in yields greater than 80% and did not require chromatographic purification (for liquid chromatography–mass spectrometry and ^{1}H nuclear magnetic resonance (NMR) spectroscopic analyses, see Supplementary Figs. 3–5). Neither larger macrocycles nor linear or polymeric products were observed. The presence of TFA was important for effective macrocyclization, which suggests that the trifluoroacetate anion coordinates to the thiourea and ammonium moieties and preorganizes the two oligoproline halves for cyclization[34]. Circular dichroism spectroscopic analyses confirmed the expected PPII helicity (minimum at ~208 nm and maximum at ~225 nm; Supplementary Fig. 6) of the oligoproline moieties in templates **T1**–**T3**.

MAHTs are prone to unproductive decarboxylation without concomitant C–C bond formation and hydrolysis of the thioester in protic solvents and at elevated temperatures[31,35]. We therefore performed the templated oligomerization reactions with bifunctional monomer **1** (prepared from *para*-hydroxybenzaldehyde, Supplementary Fig. 7) in a mixture of CH_2Cl_2:dimethylsulfoxide (DMSO) (20:1), at −10 °C and at a concentration of 10 mM (Fig. 4a). Under these conditions, mainly oligomers are formed along with a small amount of disulphide **2** that arises from hydrolysis and oxidation of **1**.

In the presence of 10 mol% of the macrocyclic templates **T1**–**T3**, complete consumption of monomer **1** took place. Organocatalytic reactions between MAHTs and aldehydes typically require catalyst loadings of 20–30% to reach full conversion within a similar time period[32,33].

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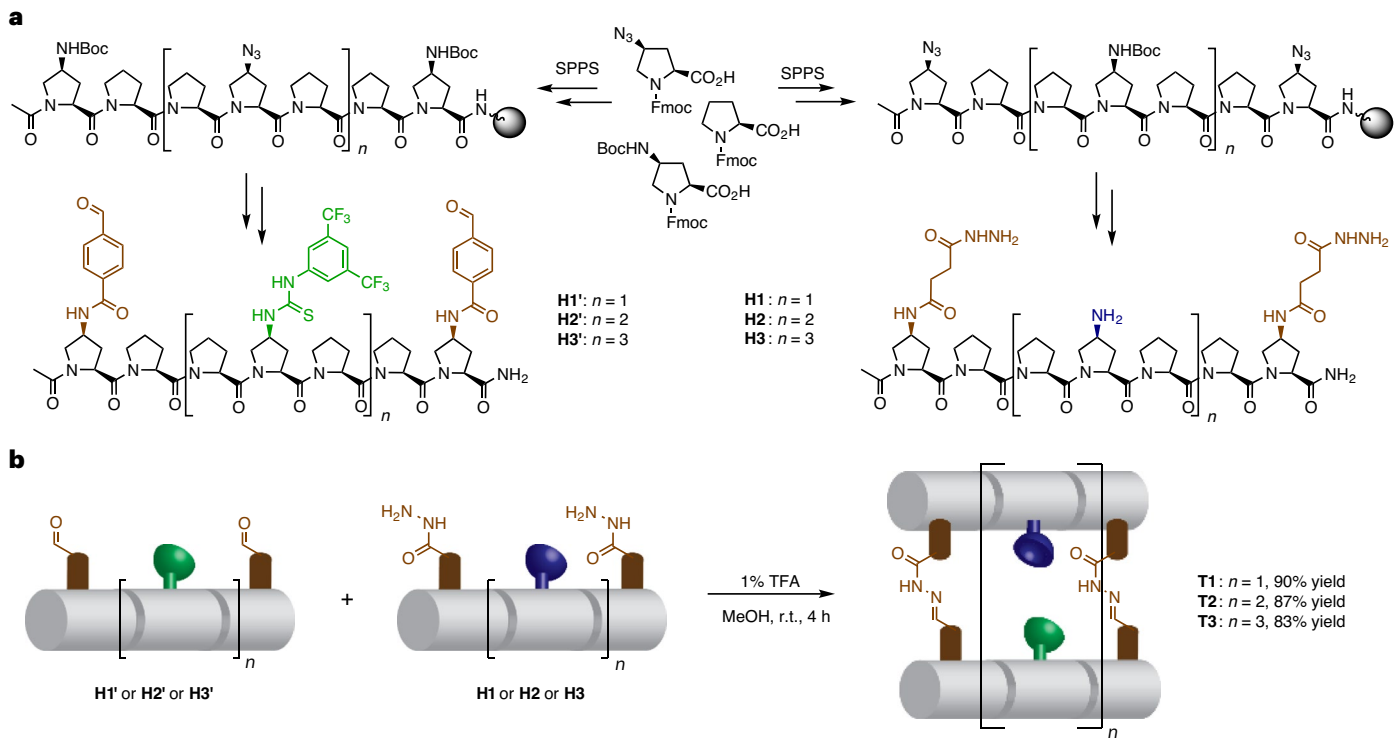

Fig. 3 | Synthesis of macrocyclic templates T1–T3. a, SPPS of half-macrocycles **H1**–**H3** and **H1'**–**H3'**. **b**, Macrocylization of **H1**–**H3** and **H1'**–**H3'** to templates **T1**–**T3**. Boc, *tert*-butoxycarbonyl; Fmoc, fluorenylmethoxycarbonyl; r.t., room temperature.

Thus, the reactivity of the templates is comparable to that of conventional organocatalysts. Size exclusion chromatography analysis of the products and comparison of the data with pure, authentic samples of di-, tri- and tetrameric oligomers **O1**–**O3** revealed a remarkable control over the length during the oligomerization process (Fig. 4b): template **T1** oligomerized **1** only into dimer **O1**, template **T2** formed predominantly trimer **O2** (77%) along with traces of tetramer **O3** (**O2**/**O3** 25:1) and the largest template **T3** produced primarily tetramer **O3** (66%) together with a smaller amount of trimer **O2** (**O3**/**O2** 5:1). The identity of the products, which formed with an enantioselectivity of 20–30% enantiomeric excess (Supplementary Figs. 8 and 9), was further confirmed by ^{1}H NMR spectroscopic and mass spectrometric analyses of the reaction mixtures and of the pure products after chromatographic separation (Fig. 4c and Supplementary Fig. 10). Thus, to the best of our knowledge, **T1**–**T3** represent the first catalysts that allow for length-controlled templated oligomerization. The number of catalytic sites within the template correlates with the length of the oligomer (Fig. 4d). Such a catalytic process is fundamentally different from previous oligomerizations, for example via aldol reactions, which used either controlled polymerization or iterative approaches[22,36–38].

Control experiments that used 'half-macrocycles' bearing only thiourea or amine moieties led to little conversion of monomer **1** and the predominant formation of disulphide **2** (Supplementary Figs. 11e,f and 12e,f). A proline hexamer with primary amine and thiourea groups at Pro^2 and Pro^5 partially converted the starting material to disulphide **2** and traces of dimer **O1** (Supplementary Figs. 11g and 12g). Similar results were obtained with a catalyst where the amine and thiourea functionalities were separated by a long flexible linker (Supplementary Figs. 11h and 12h). Furthermore, Takemoto's catalyst, a powerful catalyst for reactions of MAHTs with electrophiles[39] that bears a tertiary amine and a thiourea group, caused almost exclusive decarboxylation of monomer **1** (Supplementary Figs. 11i and 12i). A derivative of Takemoto's catalyst, with a primary instead of a tertiary amine moiety, polymerized the starting material without any length control (Fig. 4c, bottom). The same uncontrolled oligomerization was observed in the presence of bifunctional cinchona alkaloid catalysts with amine and thiourea moieties (Supplementary Figs. 11j,k and 12j,k). These results show that the length control observed in the oligomerization of **1** by catalysts **T1**–**T3** arises from the structural rigidity of the macrocyclic template and the spatial alignment of the catalytic functionalities inside the macrocyclic cavity. **T1**–**T3** allow access to oligomers of **1** in a one-pot process, which is more efficient than conventional stepwise synthesis. For example, **O2** is produced with 54% yield in a single synthetic step when using catalyst **T2**, whereas four synthetic steps with a total reaction time of 8 days are necessary to prepare **O2** from a protected derivative of **1** with an overall yield of 21% (Supplementary Fig. 13).

Titration experiments in CD_2Cl_2: DMSO-d_6 (20:1), the same conditions as used for the catalysis, revealed a binding constant of $K_a = 23.0 \pm 3.0\ M^{-1}$ for the interaction between template **T1** and substrate **1**, and a K_a of $8.1 \pm 1.3\ M^{-1}$ for the interaction between the product **O1** and **T1** (Supplementary Figs. 14 and 15). This approximately threefold lower affinity corroborates that the product binds less tightly than the monomers to the template, thus enabling catalytic turnover.

Conclusions

In conclusion, we have created fully synthetic templates capable of constructing linear oligomers from monomeric building blocks in a catalytic one-pot process. The templates can be programmed to produce oligomers of specific lengths by the choice of their dimensions and the number of catalytic sites installed within their cavities. Controlled product formation is achieved through multiple recognition and activation events that facilitate the catalytic process. Thus, the templates serve a dual role of bringing the monomeric components together and catalysing the covalent bond formation reaction between them. These results provide basic insights into the principles of catalysis and oligomerization, key processes for the evolution of life, and should

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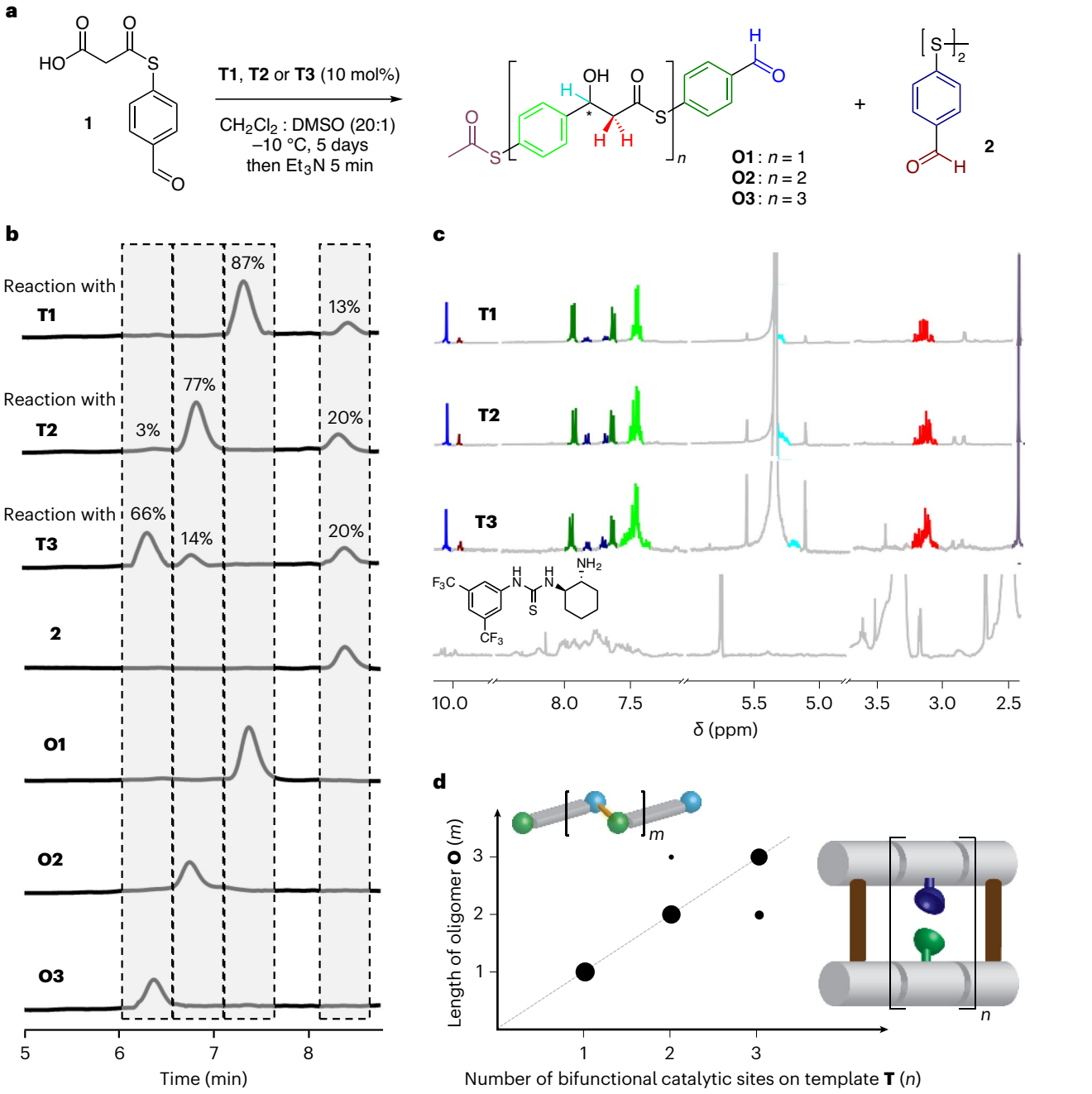

Fig. 4 | Oligomerization reactions of 1 catalysed by templates T1–T3. **a**, Reaction scheme. Note the terminal MAHT functionality of the oligomers was decarboxylated by NEt_3 to yield stable thioacetate products for analysis. **b**, Size exclusion chromatographic (SEC) analysis of the product mixtures (top to bottom: reactions catalysed by **T1**, **T2** and **T3**) and of reference samples (top to bottom: disulphide **2**, dimer **O1**, trimer **O2**, tetramer **O3**). **c**, ^{1}H NMR spectra of the product mixtures from reactions catalysed by templates **T1**–**T3** and Takemoto catalyst (CD_2Cl_2, selected regions, colour-coding corresponds to Fig. 4a). **d**, Correlation between the number of activation sites on the template and the length of the formed oligomer.

inspire future research on the controlled construction of complex molecules from individual components.

Methods

General protocols for SPPS and off-resin functionalization

The equivalents reported in the procedures refer to the loading of the resin used for SPPS.

N-terminal acetylation

Et_3N (30 equiv.) and Ac_2O (50 equiv.) were added to the amino-functionalized resin suspended in CH_2Cl_2, the mixture was agitated for 15 min and then washed with CH_2Cl_2 (5×).

Staudinger reduction of azide groups

A PMe_3 solution (1 M) in tetrahydrofuran (THF) (15 equiv. per azido group on the peptide) and H_2O (65 equiv. per azido group of the peptide) was added to the resin suspended in THF. The mixture was agitated for 2.5 h. The solvent was removed and the resin was washed with THF (3×), dimethylformamide (DMF) (3×), CH_2Cl_2 (3×), DMF (3×) and CH_2Cl_2 (3×).

Formation of thiourea groups

We added 3,5-bis-trifluoromethyl-phenylisothiocyanate (4 equiv. per amino group of the peptide) and diisopropylethylamine (8 equiv. per amino group of the peptide) to the resin suspended in CH_2Cl_2. The mixture was agitated for 90 min and then washed with CH_2Cl_2 (5×).

Attachment of hydrazide building blocks

For this protocol, 4-(2-(*tert*-butoxycarbonyl)hydrazineyl)-4-oxobutanoic acid (**7**) (4 equiv. per amino group of the peptide) and hexafluorophosphate azabenzotriazole tetramethyl uronium (HATU) (4 equiv. per amino group of the peptide) were dissolved in DMF. After 5 min they were added to the resin suspended in DMF, followed by diisopropylethylamine (8 equiv. per amino group of the peptide). The mixture was agitated for 90 min and then washed with DMF (5×) and CH_2Cl_2 (5×).

Cleavage from the solid support and side-chain deprotection of the peptides

The resin was agitated for 1 h in a mixture of TFA/CH_2Cl_2/triisopropylsilane (90:7.5:2.5) and the solution was collected by filtration. The filtrate was concentrated to a small volume under reduced pressure and the product was precipitated from cold Et_2O. The white solid was isolated by centrifugation of the suspension and by decanting the supernatant. The solid was triturated with Et_2O twice and the residual white solid was dried under a stream of nitrogen, dissolved in H_2O/CH_3CN 1:1 and lyophilized to obtain the desired peptide as a white solid.

High-performance liquid chromatography purifications

CH_3CN (solvent A) and water containing 1% of CH_3CN and 0.1% of TFA (solvent B) were used as eluents. A flow rate of 6 ml min^{-1}, at 50 °C, was used for preparative high-performance liquid chromatography. Ultraviolet–visible monitoring was carried out at 214 nm. After purification, pure fractions were combined and all volatiles were removed by lyophilization.

Desalting of the peptides

The peptide TFA salt was dissolved in methanol. The solution was filtered through a Stratospheres XP desalting cartridge (preactivated with methanol). The cartridge was washed with methanol (4×). All volatiles of the collected fractions were evaporated under reduced pressure.

Coupling of the acetal-protected benzaldehyde moieties

The purified peptide with amino functionalities at both terminal proline residues (1 equiv.) and 4-(1,3-dioxolan-2-yl)benzoic acid pentafluorophenyl ester (**7**) (8 equiv.) were dissolved in CH_2Cl_2. Diisopropylethylamine (8 equiv.) was added and the mixture was stirred at room temperature overnight. Afterwards, the volatiles were removed under reduced pressure and the crude residue was washed with Et_2O (3×) to remove excess of **7**. The crude product was used in the next step without further purification.

Cleavage of the acetal groups

The peptide (50 µmol) was dissolved in methanol (2 ml) and a 1 N aqueous HCl solution was added (2 ml). The solution was stirred at room temperature for 3 h. Then CH_2Cl_2 (5 ml) and H_2O (5 ml) were added. The layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 ml). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated. The product was purified by filtration over a plug of silica using CH_2Cl_2:MeOH (5:1) as eluent.

General protocol for the macrocyclization reactions

The two half-macrocycles (20 µmol each) were dissolved in methanol (10 ml). TFA (100 µl) was added and the mixture was stirred at room temperature for 4 h. Then, all volatiles were removed under reduced pressure and the crude solid was washed with diethyl ether (2 × 5 ml) and CH_2Cl_2 (2 × 5 ml). The product was desalted and then used directly in the templated oligomerization reactions. Note, it is important to perform the macrocyclization reaction at a 2 mM concentration of both starting materials. At lower concentration, the reaction proceeds cleanly, but at a considerably lower rate. Increasing the concentration resulted in the formation of side products, for example, larger oligomers.

General protocol for the templated oligomerization reactions

The bifunctional substrate **1** (2.25 mg, 10 µmol) was dissolved in CH_2Cl_2:DMSO = 20:1 (0.1 ml). The solution was then added to a solution of the macrocyclic template (1 µmol) in CH_2Cl_2:DMSO = 20:1 (0.9 ml) at −10 °C. The reaction was subsequently stirred at −10 °C for 5 days. Then, triethylamine (1.5 µl, 10 µmol) was added and the reaction was allowed to warm to room temperature. The volatiles were removed under reduced pressure, without heating. The residue was redissolved in CH_2Cl_2 and filtered through a plug of silica. The silica plug was washed with CH_2Cl_2:MeOH = 50:1 and the collected filtrates were concentrated.

Data availability

The authors declare that the data supporting the findings of this study are available in the article and its Supplementary Information.

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Author contributions

B.L. and H.W. conceptualized the project and wrote the manuscript. B.L. carried out the experimental work, with support from D.S., R.B. and D.Z. for the synthesis of the templates and monomer **1**. M.S. performed computational studies.

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Competing interests

The authors declare no competing interests.

Additional information

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Correspondence and requests for materials should be addressed to Bartosz M. Lewandowski or Helma Wennemers.

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