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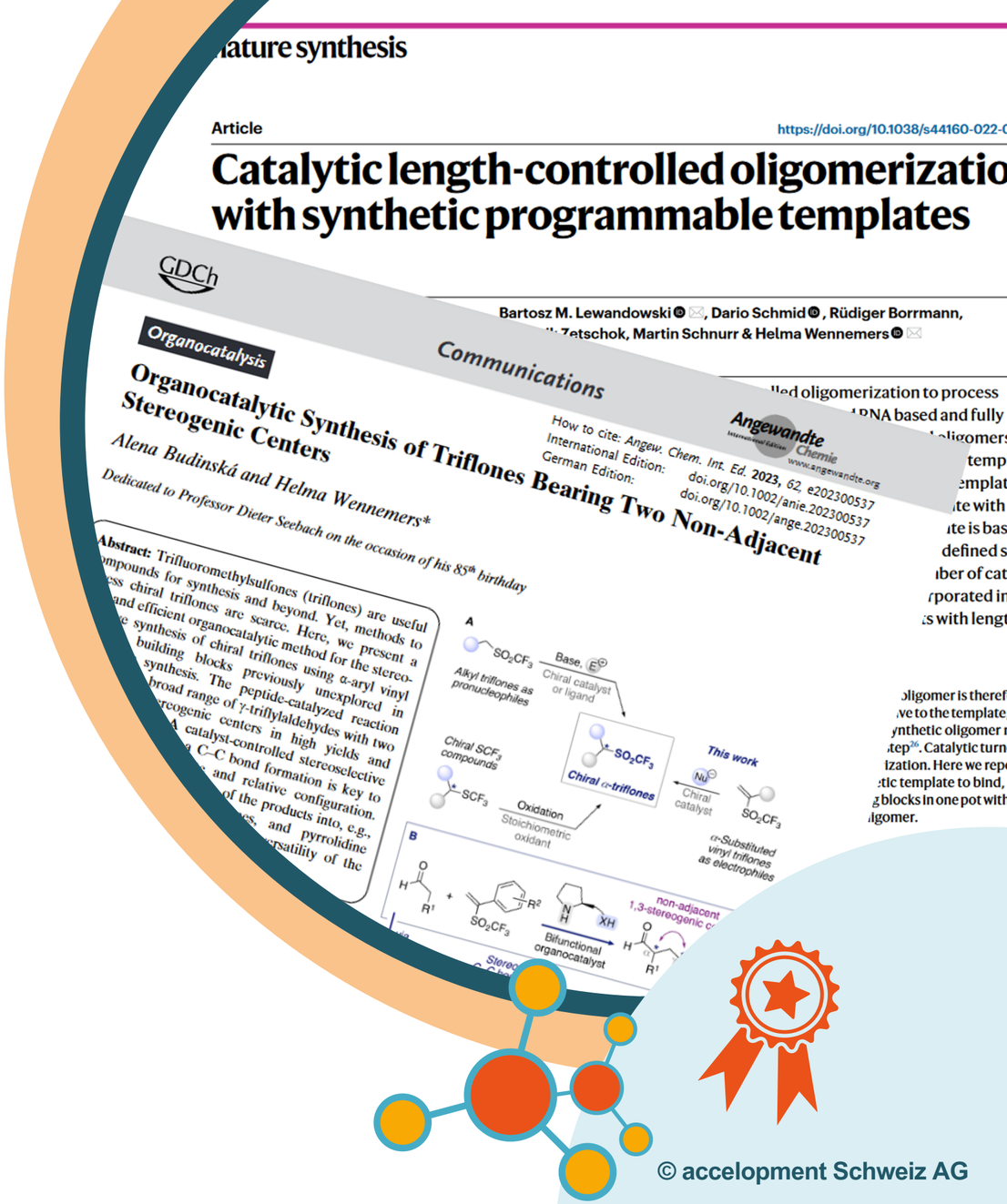

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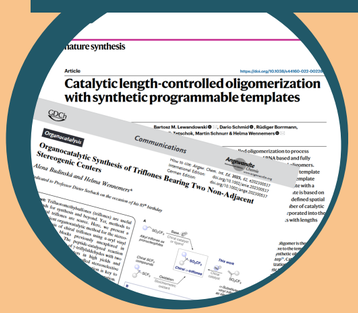

2020

1 — *"Amine Catalysis with Substrates Bearing N-Heterocyclic Moieties Enabled by Control over the Enamine Pyramidalization Direction"*

2021

2 — *"Primitive selection of the fittest emerging through functional synergy in nucleopeptide networks"*

3 — *"Reversible Photoswitchable Inhibitors Generate Ultrasensitivity in Out-Of-Equilibrium Enzymatic Reactions"*

4 — *"Reversible Photoswitchable Inhibitors Enable Wavelength-Selective Regulation of Out-of-Equilibrium Bi-Enzymatic Systems"*

5 — *"Accelerated Reaction Engineering of Photo(bio)catalytic Reactions through Parallelization with an Open-Source Photoreactor"*

6 — *"Synergistic Peptide and Gold Catalysis: Enantioselective Addition of Branched Aldehydes to Allenamides"*

2022

7 — *"Strategies for Transferring Photobiocatalysis to Continuous Flow Exemplified by Photodecarboxylation of Fatty Acids"*

8 — *"Collective Adaptability in a Replication Network of Minimal Nucleobase Sequences"*

9 — *"Tripeptide Organocatalysts for Stereoselective Conjugate Addition Reactions with N-Heterocyclic Substituents"*

10 — *"Stereoselective peptide catalysis in complex environments – from river water to cell lysates"*

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12 — *"Shortening Synthetic Routes to Small Molecule Active Pharmaceutical Ingredients Employing Biocatalytic Methods"*

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13 — *"Organocatalytic Synthesis of Triflones Bearing Two Non-Adjacent Stereogenic Centers"*

14 — *"Catalytic length-controlled oligomerization with synthetic programmable templates"*

15 — *"Dynamic exchange controls the assembly structure of nucleic-acid-peptide chimeras"*

16 — *"Modifying the catalytic activity of lipopeptide assemblies with nucleobases"*

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From the authors

Control over the enamine pyramidalization, a long-overlooked key feature, enhances the reactivity and stereoselectivity of amine catalysis. The work laid the basis for dual catalysis of peptides and enzymes and supramolecular catalysis.

1

"Amine Catalysis with Substrates Bearing N-Heterocyclic Moieties Enabled by Control over the Enamine Pyramidalization Direction"

Jasper S. Möhler, Tobias Schnitzer, Helma Wennemers.
Chem. Eur. J. 2020, 26, 15623 –15628;
DOI: 10.1002/chem.202002966Adv. Synth.Catal.2022,364

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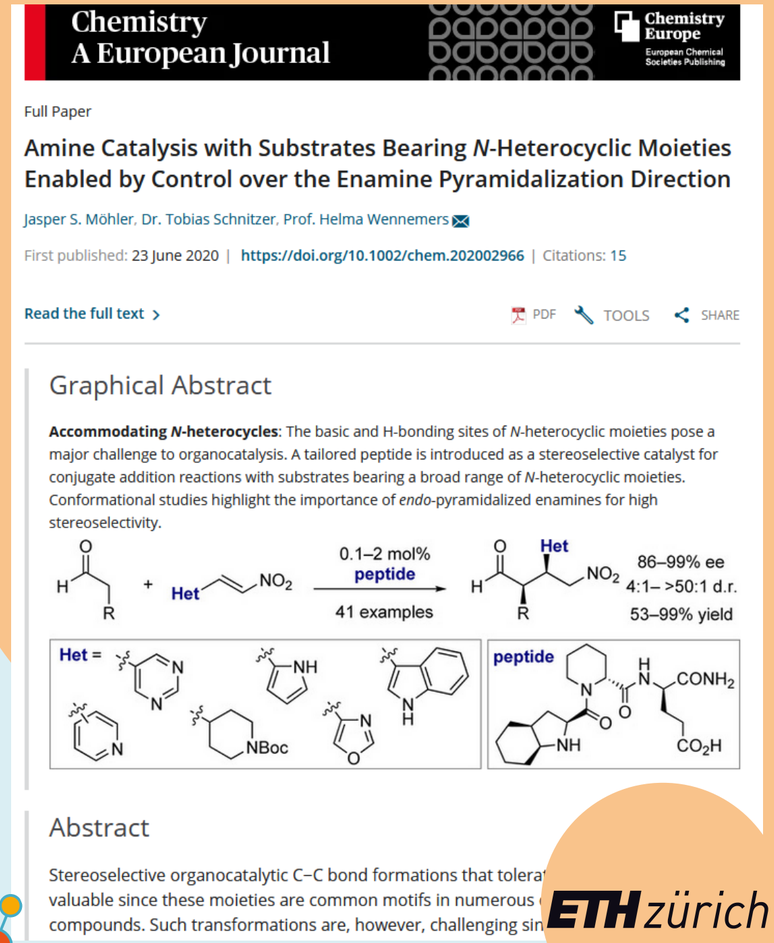

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Amine Catalysis with Substrates Bearing *N*-Heterocyclic Moieties Enabled by Control over the Enamine Pyramidalization Direction

Jasper S. Möhler, Dr. Tobias Schnitzer, Prof. Helma Wennemers

First published: 23 June 2020 | https://doi.org/10.1002/chem.202002966 | Citations: 15

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Graphical Abstract

Accommodating *N*-heterocycles: The basic and H-bonding sites of *N*-heterocyclic moieties pose a major challenge to organocatalysis. A tailored peptide is introduced as a stereoselective catalyst for conjugate addition reactions with substrates bearing a broad range of *N*-heterocyclic moieties. Conformational studies highlight the importance of *endo*-pyramidalized enamines for high stereoselectivity.

Abstract

Stereoselective organocatalytic C–C bond formations that tolera
valuable since these moieties are common motifs in numerous
compounds. Such transformations are, however, challenging sin

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This paper reveals a successful attempt to replicate simple nucleopeptide chimeras. Different mechanisms control the replication of complementary chimeras, leading to a clear selection of one over the other.

2

"Primitive selection of the fittest emerging through functional synergy in nucleopeptide networks"

Anil Kumar Bandela, Nathaniel Wagner, Hava Sadihov, Sara Morales-Reina, Agata Chotera-Ouda, Kingshuk Basu, Rivka Cohen-Luria, Andrés de la Escosura, Gonen Ashkenasy. PNAS. 2021, 118 (9) e2015285118; DOI: 10.1073/pnas.2015285118

GONEN ASHKENASY

Professor, Ben-Gurion University of the Negev,
Laboratory of Systems Chemistry

Primitive selection of the fittest emerging through functional synergy in nucleopeptide networks

Anil Kumar Bandela[a], Nathaniel Wagner[a], Hava Sadihov[a], Sara Morales-Reina[b], Agata Chotera-Ouda[a,1], Kingshuk Basu[a], Rivka Cohen-Luria[a], Andrés de la Escosura[b,c,2], and Gonen Ashkenasy[a,2]

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Edited by Ada Yonath, Weizmann Institute of Science, Rehovot, Israel, and approved December 29, 2020 (received for review July 20, 2020)

Many fundamental cellular and viral functions, including replication and translation, involve complex ensembles hosting synergistic activity between nucleic acids and proteins/peptides. There is ample evidence indicating that the chemical precursors of both nucleic acids and peptides could be efficiently formed in the prebiotic environment. Yet, studies on nonenzymatic replication, a central mechanism driving early chemical evolution, have focused largely on the activity of each class of these molecules separately. We show here that short nucleopeptide chimeras can replicate through autocatalytic and cross-catalytic processes, governed synergistically by the hybridization of the nucleobase motifs and the assembly propensity of the peptide segments. Unequal assembly-dependent replication induces clear selectivity toward the formation of a certain species within small networks of complementary nucleopeptides. The selectivity pattern may be influenced and indeed maximized to the point of almost extinction of the weakest replicator when the system is studied far from equilibrium and manipulated through changes in the physical (flow) and chemical (template and inhibition) conditions. We postulate that similar processes may have led to the emergence of the first functional nucleic-acid–peptide assemblies prior to the origin of life. Furthermore, spontaneous formation of related replicating complexes could potentially mark the initiation point for information transfer and rapid progression in complexity within primitive environments, which would have facilitated the development of a variety of functions found in extant biological assemblies.

chemical evolution | nucleic-acid–peptide conjugates | self-replication | molecular networks

The rich, highly efficient, and specific biochemistry in living cells is orchestrated by molecules belonging to a small number of families, primarily nucleic acids, proteins, fatty acids, and sugars. Many fundamental cellular and viral functions, including replication and translation, are facilitated by synergistic activity in complexes of these molecules, very often involving nucleic acids (DNA, RNA, or their constituent nucleotides/nucleobases) and proteins (or peptides/amino acids). Among the most important examples of such complexes are the nucleosome (which comprises DNA packaging units in eukaryotes), the ribosome (which translates RNA sequences into proteins), and amino acid–charged transfer RNA (*t*-RNA) conjugates (which are exploited during translation) (1–4). In order to harness such synergistic activity in synthetic materials, several groups (including the authors) have recently studied the coassembly of nucleic acids with (often) positively charged peptides or the self-assembly of premade nucleic-acid–peptide (NA–pep) chimeras (5–12). It is expected that such assemblies could produce new materials for various applications, such as autocatalysis, electron transfer, tissue scaffolding, and (drug) delivery (13–18). Intriguingly, the NA–pep assemblies combine "digital" molecular information for the hybridization of nucleic acids with "analog" instructions that affect peptide aggregation and, as such, are expected to show superior behavior in comparison with related nucleic-acid–only or peptide-only assemblies (19–21).

We now propose that alongside the development of NA–pep conjugate assemblies for new materials, an analysis of the formation of chimeras within complex mixtures, and particularly the selection of specific sequences through replication processes, will offer insight into their emergence in the early chemical evolution. Indeed, several studies have indicated that evolution in prebiotic environments, toward the origin of life, must have involved cooperative interactions among diverse classes of molecules (22–25). Other studies, including the seminal works of Eigen (26) and Kauffman (27), have revealed the possible emergence of synergistic activity in prebiotic autocatalytic networks and, as a consequence, phase transitions toward beneficial cooperative and/or selective behavior (28, 29). Importantly, while it has been shown that highly complex functions emerge by wiring together multiple pathways—driving, for example, elaborate feedback loops—our studies, as well as others, have indicated that multiple unique dynamic features (30–36), including chemical computation (37), can be developed in relatively small networks.

Despite strong evidence for prebiotic pathways that yield nucleobases and peptides—suggesting that molecules of both families were indeed present in early chemical evolution—prebiotic chemistry research has focused largely on studying each class of molecule separately (38). This approach has led to incomplete discussions on the "RNA World," the "Peptide

Significance

Research on the chemical origin of life comprises one of the most exciting topics in contemporary science. Prebiotic chemistry provided evidence that precursors of both nucleic acids and proteins might be formed in the prebiotic environment. Yet, studies on nonenzymatic replication—a central mechanism driving chemical evolution—focused largely on each class of these molecules separately. This paper reveals a successful attempt to replicate simple nucleopeptide chimeras. Most importantly, different mechanisms control the replication of complementary chimeras, leading to a clear selection of one over the other. We propose that related processes may have led to the emergence of the first functional nucleic-acid–peptide assemblies, which further developed into biological assemblies such as the ribosomes and viruses.

Author contributions: A.K.B., A.d.l.E., and G.A. designed research; A.K.B., N.W., H.S., S.M.-R., A.C.-O., and K.B. performed research; A.K.B., R.C.-L., and [illegible] data; and A.K.B., A.d.l.E., and G.A. wrote the paper.

The authors declare no competing interest.

This article is a PNAS Direct Submission.

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From the authors

This general and modular strategy enables reversible and tunable control over the kinetic rates of individual enzyme-catalyzed reactions and makes a programmable linkage of enzymes to a wide range of network topologies feasible.

3

"Reversible Photoswitchable Inhibitors Generate Ultrasensitivity in Out-Of-Equilibrium Enzymatic Reactions"

Michael Teders, Aleksandr A. Pogodaev, Glenn Bojanov, Wilhelm T. S. Huck. JACS. 2021, 143 (15), 5709–5716;
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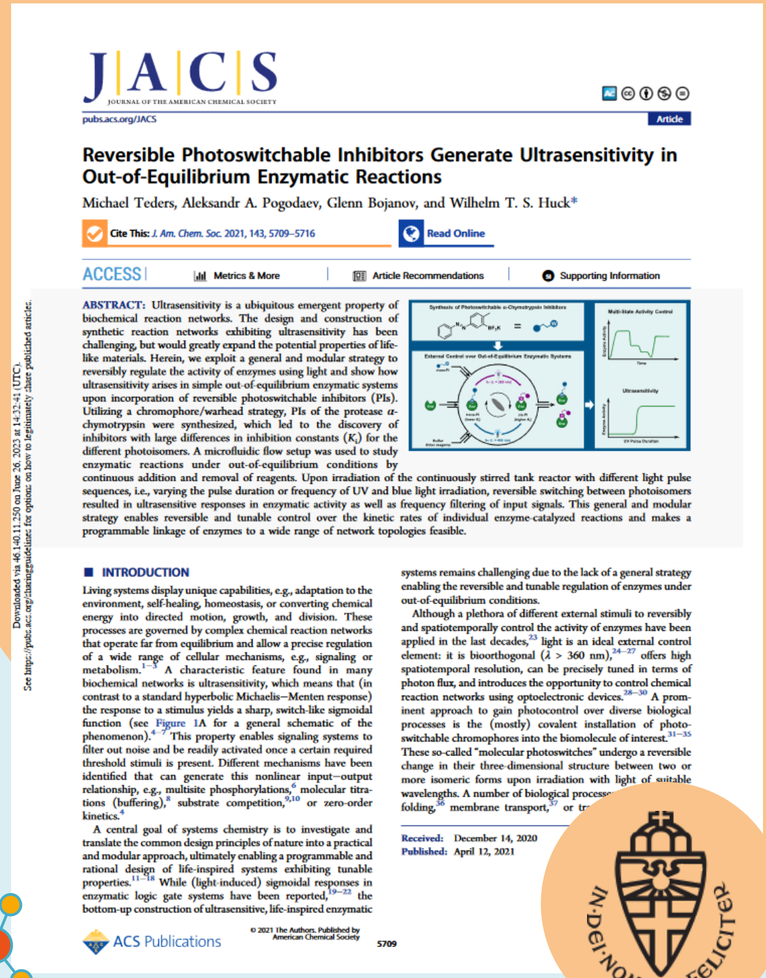

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Article

Reversible Photoswitchable Inhibitors Generate Ultrasensitivity in Out-of-Equilibrium Enzymatic Reactions

Michael Teders, Aleksandr A. Pogodaev, Glenn Bojanov, and Wilhelm T. S. Huck*

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ABSTRACT: Ultrasensitivity is a ubiquitous emergent property of biochemical reaction networks. The design and construction of synthetic reaction networks exhibiting ultrasensitivity has been challenging, but would greatly expand the potential properties of life-like materials. Herein, we exploit a general and modular strategy to reversibly regulate the activity of enzymes using light and show how ultrasensitivity arises in simple out-of-equilibrium enzymatic systems upon incorporation of reversible photoswitchable inhibitors (PIs). Utilizing a chromophore/warhead strategy, PIs of the protease α-chymotrypsin were synthesized, which led to the discovery of inhibitors with large differences in inhibition constants (K_i) for the different photoisomers. A microfluidic flow setup was used to study enzymatic reactions under out-of-equilibrium conditions by continuous addition and removal of reagents. Upon irradiation of the continuously stirred tank reactor with different light pulse sequences, i.e., varying the pulse duration or frequency of UV and blue light irradiation, reversible switching between photoisomers resulted in ultrasensitive responses in enzymatic activity as well as frequency filtering of input signals. This general and modular strategy enables reversible and tunable control over the kinetic rates of individual enzyme-catalyzed reactions and makes a programmable linkage of enzymes to a wide range of network topologies feasible.

■ **INTRODUCTION**

Living systems display unique capabilities, e.g., adaptation to the environment, self-healing, homeostasis, or converting chemical energy into directed motion, growth, and division. These processes are governed by complex chemical reaction networks that operate far from equilibrium and allow a precise regulation of a wide range of cellular mechanisms, e.g., signaling or metabolism.[1−3] A characteristic feature found in many biochemical networks is ultrasensitivity, which means that (in contrast to a standard hyperbolic Michaelis−Menten response) the response to a stimulus yields a sharp, switch-like sigmoidal function (see Figure 1A for a general schematic of the phenomenon).[4−7] This property enables signaling systems to filter out noise and be readily activated once a certain required threshold stimuli is present. Different mechanisms have been identified that can generate this nonlinear input−output relationship, e.g., multisite phosphorylations,[6] molecular titrations (buffering),[8] substrate competition,[9,10] or zero-order kinetics.[4]

A central goal of systems chemistry is to investigate and translate the common design principles of nature into a practical and modular approach, ultimately enabling a programmable and rational design of life-inspired systems exhibiting tunable properties.[11−18] While (light-induced) sigmoidal responses in enzymatic logic gate systems have been reported,[19−22] the bottom-up construction of ultrasensitive, life-inspired enzymatic systems remains challenging due to the lack of a general strategy enabling the reversible and tunable regulation of enzymes under out-of-equilibrium conditions.

Although a plethora of different external stimuli to reversibly and spatiotemporally control the activity of enzymes have been applied in the last decades,[23] light is an ideal external control element: it is bioorthogonal (λ > 360 nm),[24−27] offers high spatiotemporal resolution, can be precisely tuned in terms of photon flux, and introduces the opportunity to control chemical reaction networks using optoelectronic devices.[28−30] A prominent approach to gain photocontrol over diverse biological processes is the (mostly) covalent installation of photoswitchable chromophores into the biomolecule of interest.[31−35] These so-called "molecular photoswitches" undergo a reversible change in their three-dimensional structure between two or more isomeric forms upon irradiation with light of suitable wavelengths. A number of biological processes, [illegible] folding,[36] membrane transport,[37] or tr[illegible]

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From the authors

We have successfully exploited a general and modular strategy to control functional enzymatic systems under out-of-equilibrium conditions via the incorporation of competitive photoswitchable trypsin and α-chymotrypsin inhibitors.

4

"Reversible Photoswitchable Inhibitors Enable Wavelength-Selective Regulation of Out-of-Equilibrium Bi-Enzymatic Systems"

Michael Teders, Nicholas M. Murray, Wilhelm T. S. Huck.
ChemSystemsChem. 2021;
DOI: 10.1002/syst.202100020

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Professor, Radboud University, Huck Research Group

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Reversible Photoswitchable Inhibitors Enable Wavelength-Selective Regulation of Out-of-Equilibrium Bi-enzymatic Systems

Michael Teders, Nicholas R. Murray, and Wilhelm T. S. Huck*[a]

The construction of synthetic enzymatic reaction networks can provide new insights into the design principles of living systems. However, the programmable connection of enzymes into a wide range of network topologies has been challenging due to the lack of a general strategy enabling a reversible activity regulation of individual network enzymes. Here, we exploit a general and modular strategy based on the external regulation of enzymes using light and photoswitchable inhibitors (PIs) that enables the bottom-up construction and control of enzymatic systems studied under out-of-equilibrium conditions. Upon synthesis and incorporation of potent photoswitchable trypsin inhibitors (Tr-PIs), the output of several functional enzymatic systems could be photoregulated using 390/460 nm light as a trigger signal. In addition, the wavelength-selective control over the activity of two enzymes within a functional bi-enzymatic system was achieved using a suitable combination of two PIs.

1. Introduction

In living systems, biochemical processes are organized into complex networks, which are continuously sensing and adapting to changes in the environment.[1] The properties of these networks underlie many of the characteristic capabilities of living systems, such as self-healing, homeostasis, or conversion of chemical energy into directed motion, growth and division.[2–4]

A central goal of systems chemistry is to investigate and translate the common design principles of the enzymatic reaction networks found in nature into a practical and modular approach, thereby ultimately enabling the programmable and rational design of life-inspired systems exhibiting tunable properties.[5–14] In living systems, enzymes are the molecular machines of choice as their activity can be controlled via, for example, post-translational modifications, allosteric interactions, or substrate competition.[2,15–18] In addition, their non-linearity (resulting in sensitive feedback loops), chemical specificity and high turnover numbers make them ideal for converting a wide range of signals into a molecular output. However, the bottom-up construction of (complex) life-inspired systems is particularly challenging due to the lack of a general strategy enabling the reversible and precise regulation of individual network components (e.g., enzymes) and isolated network motifs.

A plethora of different strategies to reversibly and spatiotemporally control the activity of enzymes have been developed in the past decades.[19–26] In a systems chemistry setting, light is an ideal external trigger to regulate enzyme activity,[27,28] and we recently reported that the incorporation of reversible photoswitchable α-chymotrypsin inhibitors (Cr-PIs) generates a non-linear ultrasensitive input-output response when studying enzymatic reactions under out-of-equilibrium conditions.[29] Here, we expand upon our strategy by synthesizing photoswitchable trypsin inhibitors (Tr-PIs) and combining these in the bottom-up construction of photoresponsive modules containing two enzymes (Figure 1). To demonstrate the feasibility of our strategy to control multiple enzymes individually using different wavelengths, we incorporated both a Cr- and a Tr-PI in a bi-enzymatic system.

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Supporting information for this article is available on the WWW under https://doi.org/10.1002/syst.202100020

Figure 1. Reversible photocontrol o… by the incorporation of photoswitch… Sub—substrate, FS—fluorogenic sub… tem.

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From the authors

Working with light-dependent enzymatic reactions is challenging due to the need for specialized illumination equipment. Here, we introduce our open-source photoreactor, enabling precise illumination for 24 samples with controlled agitation, temperature, wavelength, and light intensity.

5

"Accelerated Reaction Engineering of Photo(bio)catalytic Reactions through Parallelization with an Open-Source Photoreactor"

Christoph Winkler, Stefan Simić, Valentina Jurkaš, Sarah Bierbaumer, Luca Schmermund, Silvan Poschenrieder, Sarah A. Berger, Elisa Kulterer, Robert Kourist, and Wolfgang Kroutil. ChemPhotoChem. 2021, 05;
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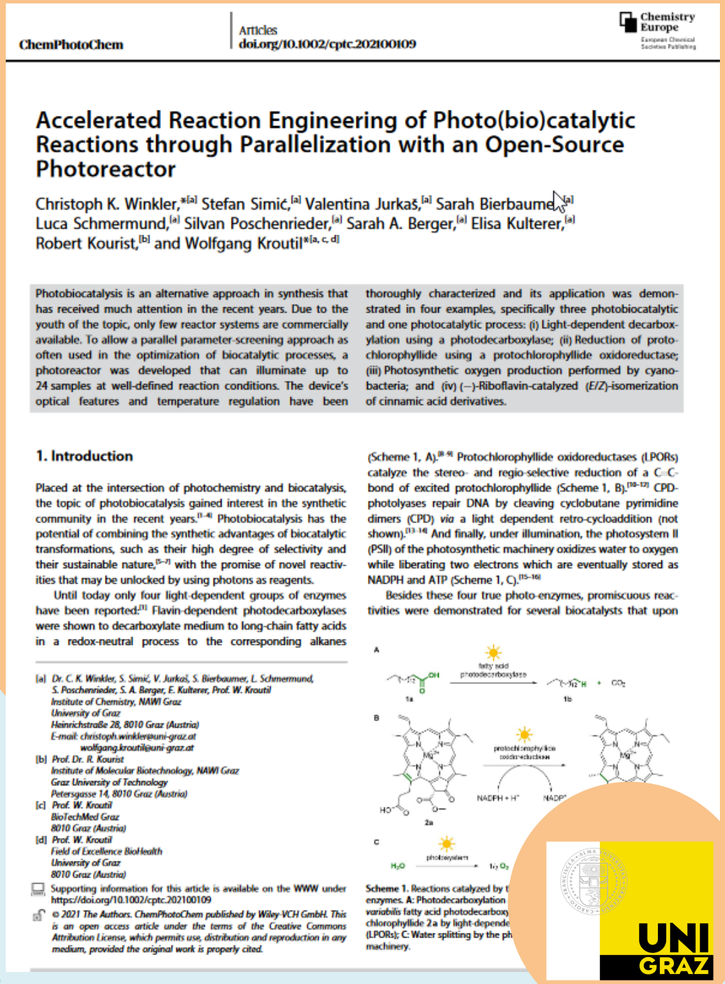

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Accelerated Reaction Engineering of Photo(bio)catalytic Reactions through Parallelization with an Open-Source Photoreactor

Christoph K. Winkler,*[a] Stefan Simić,[a] Valentina Jurkaš,[a] Sarah Bierbaumer,[a] Luca Schmermund,[a] Silvan Poschenrieder,[a] Sarah A. Berger,[a] Elisa Kulterer,[a] Robert Kourist,[b] and Wolfgang Kroutil*[a, c, d]

Photobiocatalysis is an alternative approach in synthesis that has received much attention in the recent years. Due to the youth of the topic, only few reactor systems are commercially available. To allow a parallel parameter screening approach as often used in the optimization of biocatalytic processes, a photoreactor was developed that can illuminate up to 24 samples at well-defined reaction conditions. The device's optical features and temperature regulation have been thoroughly characterized and its application was demonstrated in four examples, specifically three photobiocatalytic and one photocatalytic process: (i) Light-dependent decarboxylation using a photodecarboxylase; (ii) Reduction of protochlorophyllide using a protochlorophyllide oxidoreductase; (iii) Photosynthetic oxygen production performed by cyanobacteria; and (iv) (−)-Riboflavin-catalyzed (*E*/*Z*)-isomerization of cinnamic acid derivatives.

1. Introduction

Placed at the intersection of photochemistry and biocatalysis, the topic of photobiocatalysis gained interest in the synthetic community in the recent years.[1–4] Photobiocatalysis has the potential of combining the synthetic advantages of biocatalytic transformations, such as their high degree of selectivity and their sustainable nature,[5–7] with the promise of novel reactivities that may be unlocked by using photons as reagents.

Until today only four light-dependent groups of enzymes have been reported:[2] Flavin-dependent photodecarboxylases were shown to decarboxylate medium to long-chain fatty acids in a redox-neutral process to the corresponding alkanes (Scheme 1, A).[8–10] Protochlorophyllide oxidoreductases (LPORs) catalyze the stereo- and regio-selective reduction of a C=C-bond of excited protochlorophyllide (Scheme 1, B).[10–12] CPD-photolyases repair DNA by cleaving cyclobutane pyrimidine dimers (CPD) *via* a light dependent retro-cycloaddition (not shown).[13–14] And finally, under illumination, the photosystem II (PSII) of the photosynthetic machinery oxidizes water to oxygen while liberating two electrons which are eventually stored as NADPH and ATP (Scheme 1, C).[15–16]

Besides these four true photo-enzymes, promiscuous reactivities were demonstrated for several biocatalysts that upon

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Supporting information for this article is available on the WWW under https://doi.org/10.1002/cptc.202100109

Scheme 1. Reactions catalyzed by t… enzymes. A: Photodecarboxylation … variabilis fatty acid photodecarbox… chlorophyllide 2a by light-depende… (LPORs); C: Water splitting by the ph… machinery.

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From the authors

How robust can stereoselective peptide catalysts, "mini-enzymes", be? In this publication, we show that peptide catalysis can work in concert with gold-catalysis.

6

"Synergistic Peptide and Gold Catalysis: Enantioselective Addition of Branched Aldehydes to Allenamides"

Helma Wennemers, Leo D. M. Nicholls.
Chem. Eur. J. 2021, 03;
DOI: 10.1002/chem.202103197

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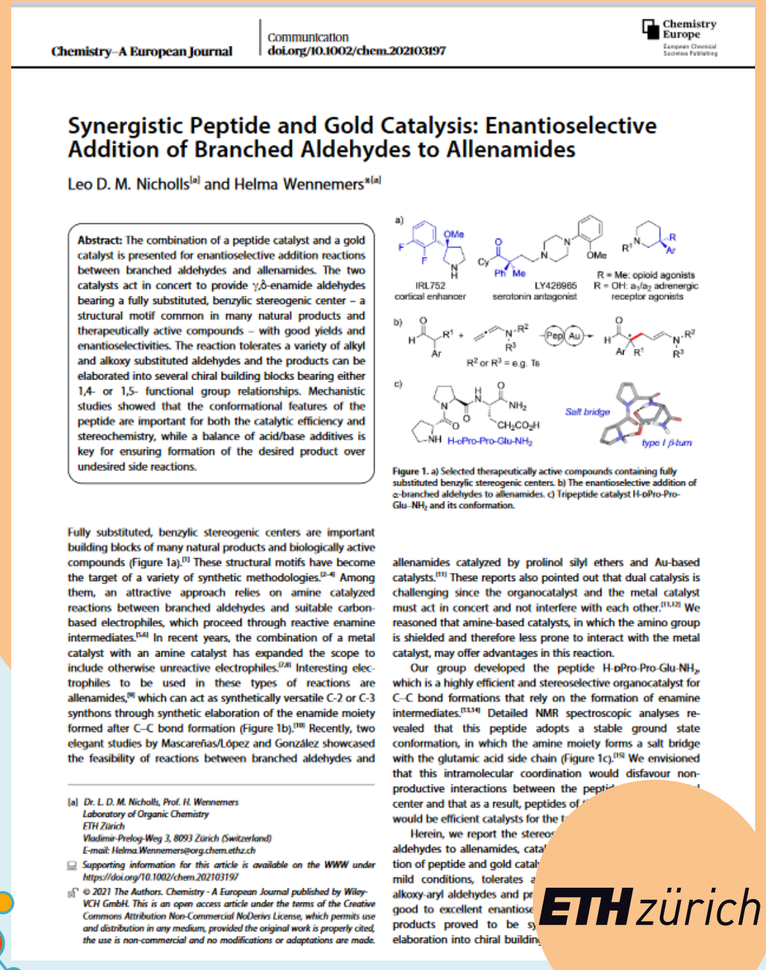

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Synergistic Peptide and Gold Catalysis: Enantioselective Addition of Branched Aldehydes to Allenamides

Leo D. M. Nicholls[a] and Helma Wennemers*[a]

Abstract: The combination of a peptide catalyst and a gold catalyst is presented for enantioselective addition reactions between branched aldehydes and allenamides. The two catalysts act in concert to provide γ,δ-enamide aldehydes bearing a fully substituted, benzylic stereogenic center – a structural motif common in many natural products and therapeutically active compounds – with good yields and enantioselectivities. The reaction tolerates a variety of alkyl and alkoxy substituted aldehydes and the products can be elaborated into several chiral building blocks bearing either 1,4- or 1,5- functional group relationships. Mechanistic studies showed that the conformational features of the peptide are important for both the catalytic efficiency and stereochemistry, while a balance of acid/base additives is key for ensuring formation of the desired product over undesired side reactions.

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Supporting information for this article is available on the WWW under https://doi.org/10.1002/chem.202103197

Figure 1. a) Selected therapeutically active compounds containing fully substituted benzylic stereogenic centers. b) The enantioselective addition of α-branched aldehydes to allenamides. c) Tripeptide catalyst H-dPro-Pro-Glu-NH_2 and its conformation.

Fully substituted, benzylic stereogenic centers are important building blocks of many natural products and biologically active compounds (Figure 1a).[1] These structural motifs have become the target of a variety of synthetic methodologies.[2–4] Among them, an attractive approach relies on amine catalyzed reactions between branched aldehydes and suitable carbon-based electrophiles, which proceed through reactive enamine intermediates.[5,6] In recent years, the combination of a metal catalyst with an amine catalyst has expanded the scope to include otherwise unreactive electrophiles.[7,8] Interesting electrophiles to be used in these types of reactions are allenamides,[9] which can act as synthetically versatile C-2 or C-3 synthons through synthetic elaboration of the enamide moiety formed after C–C bond formation (Figure 1b).[10] Recently, two elegant studies by Mascareñas/López and González showcased the feasibility of reactions between branched aldehydes and allenamides catalyzed by prolinol silyl ethers and Au-based catalysts.[11] These reports also pointed out that dual catalysis is challenging since the organocatalyst and the metal catalyst must act in concert and not interfere with each other.[11,12] We reasoned that amine-based catalysts, in which the amino group is shielded and therefore less prone to interact with the metal catalyst, may offer advantages in this reaction.

Our group developed the peptide H-dPro-Pro-Glu-NH_2, which is a highly efficient and stereoselective organocatalyst for C–C bond formations that rely on the formation of enamine intermediates.[13,14] Detailed NMR spectroscopic analyses revealed that this peptide adopts a stable ground state conformation, in which the amine moiety forms a salt bridge with the glutamic acid side chain (Figure 1c).[15] We envisioned that this intramolecular coordination would disfavour non-productive interactions between the pepti… center and that as a result, peptides of … would be efficient catalysts for the …

Herein, we report the stereo… aldehydes to allenamides, cata… tion of peptide and gold catal… mild conditions, tolerates … alkoxy-aryl aldehydes and pr… good to excellent enantios… products proved to be s… elaboration into chiral buildin…

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From the authors

Photobiocatalysis is a young field of research dealing with the combination of light and enzymes to drive reactions. Here, we investigated how one of only four known natural light-dependent enzymes behaves in tubular reactors, with the aim of improving its efficiency.

7

"Strategies for Transferring Photobiocatalysis to Continuous Flow Exemplified by Photodecarboxylation of Fatty Acids"

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Strategies for Transferring Photobiocatalysis to Continuous Flow Exemplified by Photodecarboxylation of Fatty Acids

Stefan Simić, Miglė Jakštaitė, Wilhelm T. S. Huck, Christoph K. Winkler,* and Wolfgang Kroutil*

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ABSTRACT: The challenges of light-dependent biocatalytic transformations of lipophilic substrates in aqueous media are manifold. For instance, photolability of the catalyst as well as insufficient light penetration into the reaction vessel may be further exacerbated by a heterogeneously dispersed substrate. Light penetration may be addressed by performing the reaction in continuous flow, which allows two modes of applying the catalyst: (i) heterogeneously, immobilized on a carrier, which requires light-permeable supports, or (ii) homogeneously, dissolved in the reaction mixture. Taking the light-dependent photodecarboxylation of palmitic acid catalyzed by fatty-acid photodecarboxylase from *Chlorella variabilis* (*Cv*FAP) as a showcase, strategies for the transfer of a photoenzyme-catalyzed reaction into continuous flow were identified. A range of different supports were evaluated for the immobilization of *Cv*FAP, whereby Eupergit C250 L was the carrier of choice. As the photostability of the catalyst was a limiting factor, a homogeneous system was preferred instead of employing the heterogenized enzyme. This implied that photolabile enzymes may preferably be applied in solution if repair mechanisms cannot be provided. Furthermore, when comparing different wavelengths and light intensities, extinction coefficients may be considered to ensure comparable absorption at each wavelength. Employing homogeneous conditions in the *Cv*FAP-catalyzed photodecarboxylation of palmitic acid afforded a space-time yield unsurpassed by any reported batch process (5.7 $g \cdot L^{-1} \cdot h^{-1}$, 26.9 $mmol \cdot L^{-1} \cdot h^{-1}$) for this reaction, demonstrating the advantage of continuous flow in attaining higher productivity of photobiocatalytic processes.

KEYWORDS: *biocatalysis, photocatalysis, flow, decarboxylation, renewables*

■ INTRODUCTION

Although direct excitation of organic compounds by light to facilitate chemical reactions has been known for more than a century, the recent rise of photoredox catalysis has significantly expanded the scope of photochemistry in the synthesis of organic molecules.[1] Apart from enabling new reaction pathways not accessible by thermal control, the use of photon energy is also considered a sustainable approach.[2] Akin to photocatalysis, biocatalysis has been shown to enable sustainable reaction methodologies due to its generally mild reaction conditions, use of aqueous media, high stereo- and chemoselectivity, and ever-increasing substrate and reaction scope.[3]

At the interface of these two fields of catalysis, photobiocatalysis arose, whereby either the enzyme itself requires light (naturally or by promiscuity) or photoinduced electrons are transferred to it.[4] The scope of photobiocatalytic transformations was significantly expanded following the discovery of fatty-acid photodecarboxylases that catalyze light-dependent decarboxylation of fatty acids (Scheme 1).[5]

Scheme 1. Photodecarboxylation of Fatty Acids Catalyzed by the Photodecarboxylase *Cv*FAP from *Chlorella variabilis* NC64A

This class of natural photoenzymes and its most known orthologue from *C. variabilis* NC64A (*Cv*FAP) has subsequently shown great promise for the production of biofuels,[6] and apart from its natural substrates, fatty acids, the wild-type enzyme, or its variants have been demonstrated to decarboxylate hydroxy- and amino-substituted fatty acids,[7] dicarboxylic acids,[8] α-substituted carboxylic acids,[9] and the herbicide phosphinothricin.[10] In the enzyme's reaction mechanism, the decarboxylation event is triggered by a single [illegible] from the substrate's carboxylate group.

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From the authors

This work addresses essential questions for studies on the origins of life, such as which is the minimal nucleobase sequence length that may enable a rudimentary transmission of information in chemical systems or the importance of their adaptability to changes in the environment.

8

"Collective Adaptability in a Replication Network of Minimal Nucleobase Sequences"

Sonia Vela, Zulay D. Pardo Botero, Cristian Moya, Andres De la Escosura. Chem. Sci., 2022, Accepted Manuscript.
DOI: https://doi.org/10.1039/D2SC02419E

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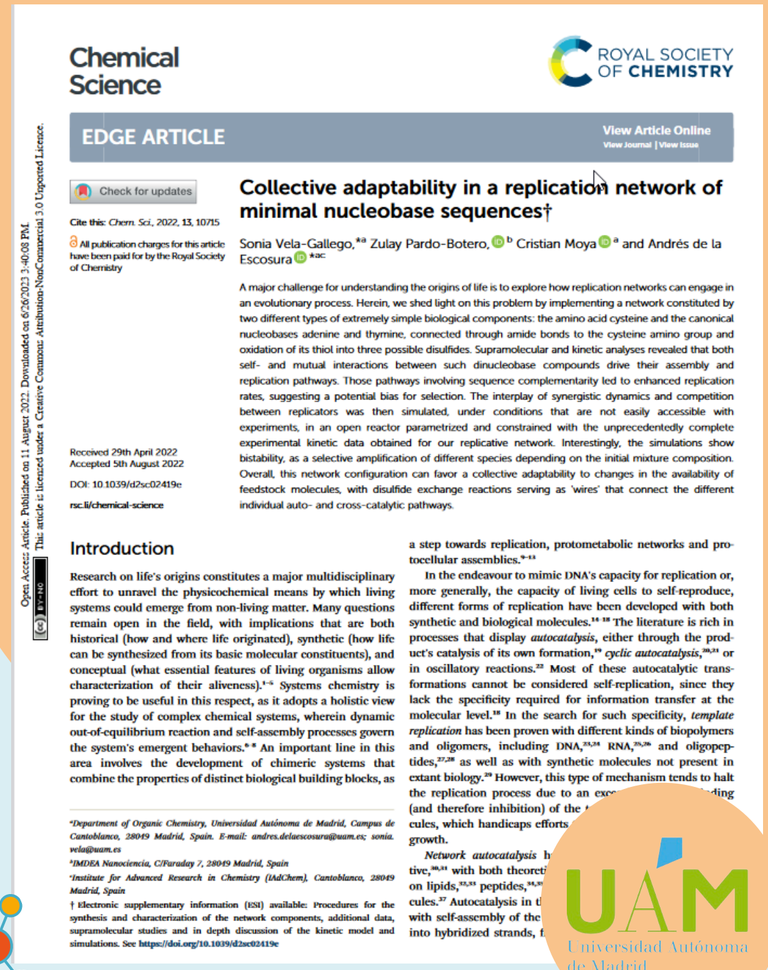

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Collective adaptability in a replication network of minimal nucleobase sequences†

Cite this: *Chem. Sci.*, 2022, **13**, 10715

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Sonia Vela-Gallego,[a,b] Zulay Pardo-Botero,[b] Cristian Moya[b,a] and Andrés de la Escosura[a,c]*

A major challenge for understanding the origins of life is to explore how replication networks can engage in an evolutionary process. Herein, we shed light on this problem by implementing a network constituted by two different types of extremely simple biological components: the amino acid cysteine and the canonical nucleobases adenine and thymine, connected through amide bonds to the cysteine amino group and oxidation of its thiol into three possible disulfides. Supramolecular and kinetic analyses revealed that both self- and mutual interactions between such dinucleobase compounds drive their assembly and replication pathways. Those pathways involving sequence complementarity led to enhanced replication rates, suggesting a potential bias for selection. The interplay of synergistic dynamics and competition between replicators was then simulated, under conditions that are not easily accessible with experiments, in an open reactor parametrized and constrained with the unprecedentedly complete experimental kinetic data obtained for our replicative network. Interestingly, the simulations show bistability, as a selective amplification of different species depending on the initial mixture composition. Overall, this network configuration can favor a collective adaptability to changes in the availability of feedstock molecules, with disulfide exchange reactions serving as 'wires' that connect the different individual auto- and cross-catalytic pathways.

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Introduction

Research on life's origins constitutes a major multidisciplinary effort to unravel the physicochemical means by which living systems could emerge from non-living matter. Many questions remain open in the field, with implications that are both historical (how and where life originated), synthetic (how life can be synthesized from its basic molecular constituents), and conceptual (what essential features of living organisms allow characterization of their aliveness).[1–5] Systems chemistry is proving to be useful in this respect, as it adopts a holistic view for the study of complex chemical systems, wherein dynamic out-of-equilibrium reaction and self-assembly processes govern the system's emergent behaviors.[6–8] An important line in this area involves the development of chimeric systems that combine the properties of distinct biological building blocks, as a step towards replication, protometabolic networks and protocellular assemblies.[9–13]

In the endeavour to mimic DNA's capacity for replication or, more generally, the capacity of living cells to self-reproduce, different forms of replication have been developed with both synthetic and biological molecules.[14–18] The literature is rich in processes that display *autocatalysis*, either through the product's catalysis of its own formation,[19] *cyclic autocatalysis*,[20,21] or in oscillatory reactions.[22] Most of these autocatalytic transformations cannot be considered self-replication, since they lack the specificity required for information transfer at the molecular level.[18] In the search for such specificity, *template replication* has been proven with different kinds of biopolymers and oligomers, including DNA,[23,24] RNA,[25,26] and oligopeptides,[27,28] as well as with synthetic molecules not present in extant biology.[29] However, this type of mechanism tends to halt the replication process due to an exc… ding (and therefore inhibition) of the … cules, which handicaps efforts … growth.

Network autocatalysis h… tive,[30,31] with both theoreti… on lipids,[32,33] peptides,[34,35] … cules.[37] Autocatalysis in t… with self-assembly of the … into hybridized strands, …

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† Electronic supplementary information (ESI) available: Procedures for the synthesis and characterization of the network components, additional data, supramolecular studies and in depth discussion of the kinetic model and simulations. See https://doi.org/10.1039/d2sc02419e

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From the authors

N-heterocycles are widespread among therapeutics and agrochemicals. For synthesis, and in particular, catalysis, these substituents are challenging since they can interfere by intermolecular interactions with the catalytic cycle. Here, we show that the activity and stereoselectivity of tailored peptide catalysts are not affected by N-heterocycles.

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"Tripeptide Organocatalysts for Stereoselective Conjugate Addition Reactions with N-Heterocyclic Substituents"

Jasper S. Möhler, Lena K. Beiersdörfer, Brenno Masina, Philipp Wechsler, Helma Wennemers. Adv. Synth.Catal. 2022, 364.
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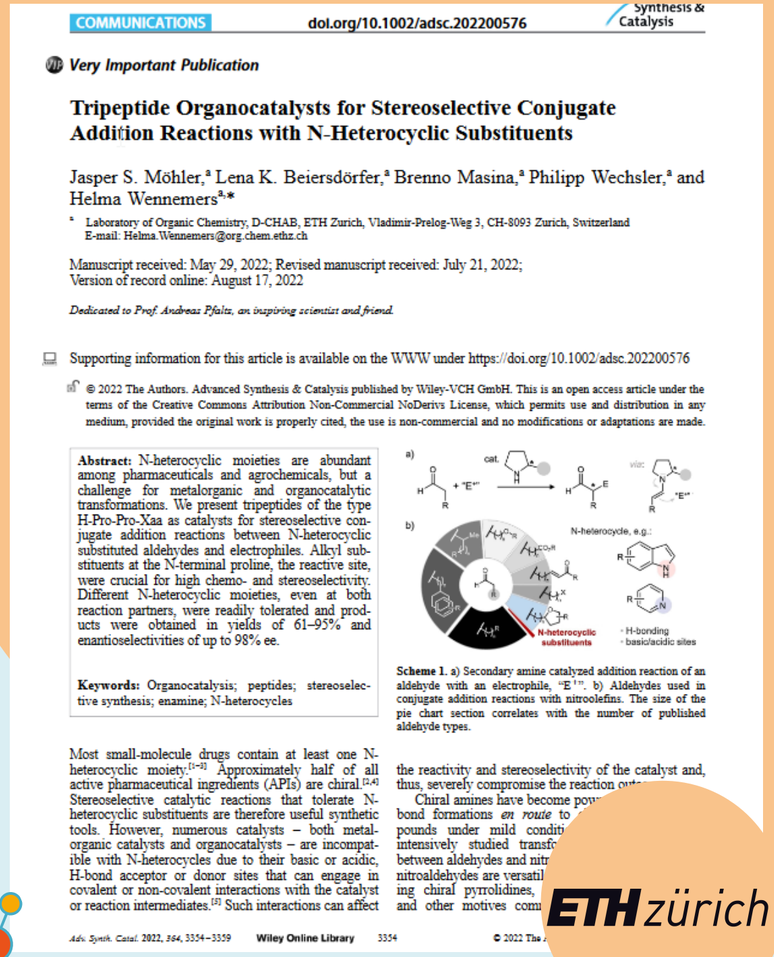
Professor, ETH Zurich, Wennemers Group



COMMUNICATIONS doi.org/10.1002/adsc.202200576 Synthesis & Catalysis

Very Important Publication

Tripeptide Organocatalysts for Stereoselective Conjugate Addition Reactions with N-Heterocyclic Substituents

Jasper S. Möhler,[a] Lena K. Beiersdörfer,[a] Brenno Masina,[a] Philipp Wechsler,[a] and Helma Wennemers[a,*]

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E-mail: Helma.Wennemers@org.chem.ethz.ch

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Dedicated to Prof. Andreas Pfaltz, an inspiring scientist and friend.

Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.202200576

Abstract: N-heterocyclic moieties are abundant among pharmaceuticals and agrochemicals, but a challenge for metalorganic and organocatalytic transformations. We present tripeptides of the type H-Pro-Pro-Xaa as catalysts for stereoselective conjugate addition reactions between N-heterocyclic substituted aldehydes and electrophiles. Alkyl substituents at the N-terminal proline, the reactive site, were crucial for high chemo- and stereoselectivity. Different N-heterocyclic moieties, even at both reaction partners, were readily tolerated and products were obtained in yields of 61–95% and enantioselectivities of up to 98% ee.

Keywords: Organocatalysis; peptides; stereoselective synthesis; enamine; N-heterocycles

Scheme 1. a) Secondary amine catalyzed addition reaction of an aldehyde with an electrophile, "E[+]". b) Aldehydes used in conjugate addition reactions with nitroolefins. The size of the pie chart section correlates with the number of published aldehyde types.

Most small-molecule drugs contain at least one N-heterocyclic moiety.[1–3] Approximately half of all active pharmaceutical ingredients (APIs) are chiral.[2,4] Stereoselective catalytic reactions that tolerate N-heterocyclic substituents are therefore useful synthetic tools. However, numerous catalysts – both metal-organic catalysts and organocatalysts – are incompatible with N-heterocycles due to their basic or acidic, H-bond acceptor or donor sites that can engage in covalent or non-covalent interactions with the catalyst or reaction intermediates.[5] Such interactions can affect the reactivity and stereoselectivity of the catalyst and, thus, severely compromise the reaction out

Chiral amines have become pow
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From the authors

Here, we investigated the properties of tripeptide catalysts in complex mixtures in hydrophobic and aqueous solvents. We challenged the catalysts with biomolecules bearing functional groups that could interfere by coordination or reaction with the peptide, the substrates, or intermediates.

10

"Stereoselective peptide catalysis in complex environments – from river water to cell lysates"

Tobias Schnitzer, Jonas W. Rackl, Helma Wennemers.
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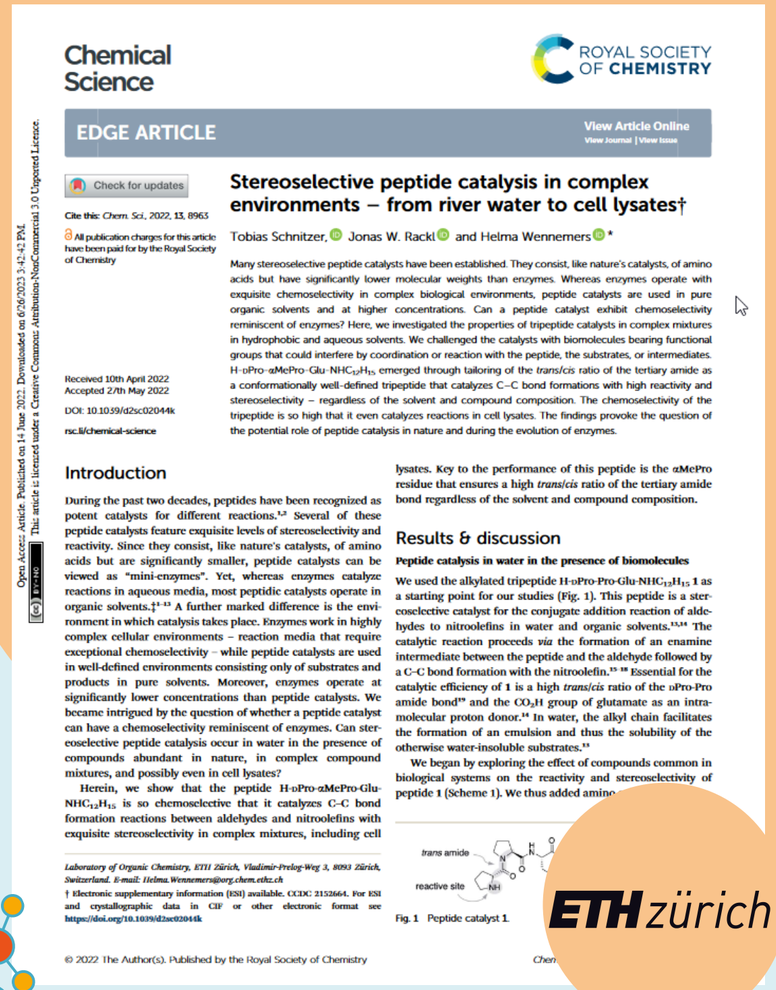

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Stereoselective peptide catalysis in complex environments – from river water to cell lysates†

Tobias Schnitzer, Jonas W. Rackl and Helma Wennemers *

Many stereoselective peptide catalysts have been established. They consist, like nature's catalysts, of amino acids but have significantly lower molecular weights than enzymes. Whereas enzymes operate with exquisite chemoselectivity in complex biological environments, peptide catalysts are used in pure organic solvents and at higher concentrations. Can a peptide catalyst exhibit chemoselectivity reminiscent of enzymes? Here, we investigated the properties of tripeptide catalysts in complex mixtures in hydrophobic and aqueous solvents. We challenged the catalysts with biomolecules bearing functional groups that could interfere by coordination or reaction with the peptide, the substrates, or intermediates. H-DPro-αMePro-Glu-$NHC_{12}H_{15}$, emerged through tailoring of the *trans*/*cis* ratio of the tertiary amide as a conformationally well-defined tripeptide that catalyzes C–C bond formations with high reactivity and stereoselectivity – regardless of the solvent and compound composition. The chemoselectivity of the tripeptide is so high that it even catalyzes reactions in cell lysates. The findings provoke the question of the potential role of peptide catalysis in nature and during the evolution of enzymes.

Introduction

During the past two decades, peptides have been recognized as potent catalysts for different reactions.[1,2] Several of these peptide catalysts feature exquisite levels of stereoselectivity and reactivity. Since they consist, like nature's catalysts, of amino acids but are significantly smaller, peptide catalysts can be viewed as "mini-enzymes". Yet, whereas enzymes catalyze reactions in aqueous media, most peptidic catalysts operate in organic solvents.[‡,3] A further marked difference is the environment in which catalysis takes place. Enzymes work in highly complex cellular environments – reaction media that require exceptional chemoselectivity – while peptide catalysts are used in well-defined environments consisting only of substrates and products in pure solvents. Moreover, enzymes operate at significantly lower concentrations than peptide catalysts. We became intrigued by the question of whether a peptide catalyst can have a chemoselectivity reminiscent of enzymes. Can stereoselective peptide catalysis occur in water in the presence of compounds abundant in nature, in complex compound mixtures, and possibly even in cell lysates?

Herein, we show that the peptide H-DPro-αMePro-Glu-$NHC_{12}H_{15}$ is so chemoselective that it catalyzes C–C bond formation reactions between aldehydes and nitroolefins with exquisite stereoselectivity in complex mixtures, including cell lysates. Key to the performance of this peptide is the αMePro residue that ensures a high *trans*/*cis* ratio of the tertiary amide bond regardless of the solvent and compound composition.

Results & discussion

Peptide catalysis in water in the presence of biomolecules

We used the alkylated tripeptide H-DPro-Pro-Glu-$NHC_{12}H_{15}$ **1** as a starting point for our studies (Fig. 1). This peptide is a stereoselective catalyst for the conjugate addition reaction of aldehydes to nitroolefins in water and organic solvents.[3,4] The catalytic reaction proceeds *via* the formation of an enamine intermediate between the peptide and the aldehyde followed by a C–C bond formation with the nitroolefin.[5–9] Essential for the catalytic efficiency of **1** is a high *trans*/*cis* ratio of the DPro-Pro amide bond[10] and the CO_2H group of glutamate as an intramolecular proton donor.[11] In water, the alkyl chain facilitates the formation of an emulsion and thus the solubility of the otherwise water-insoluble substrates.[12]

We began by exploring the effect of compounds common in biological systems on the reactivity and stereoselectivity of peptide **1** (Scheme 1). We thus added amino

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† Electronic supplementary information (ESI) available. CCDC 2152664. For ESI and crystallographic data in CIF or other electronic format see https://doi.org/10.1039/d2sc02044k

trans amide
reactive site

Fig. 1 Peptide catalyst **1**.

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From the authors

Our work presents a Bayesian analysis method which demonstrates the interference of enzyme kinetic parameters and determines most likely reaction mechanisms in artificial enzymatic networks. Moreover, enzymes immobilised in beads inside flow reactors allows us to reuse them.

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"A Bayesian Approach to Extracting Kinetic Information from Artificial Enzymatic Networks"

Mathieu G. Baltussen, Jeroen van de Wiel, Cristina Lía Fernández Regueiro, Miglė Jakštaitė and Wilhelm T. S. Huck. Anal. Chem. 2022, 94, 20, 7311–7318.
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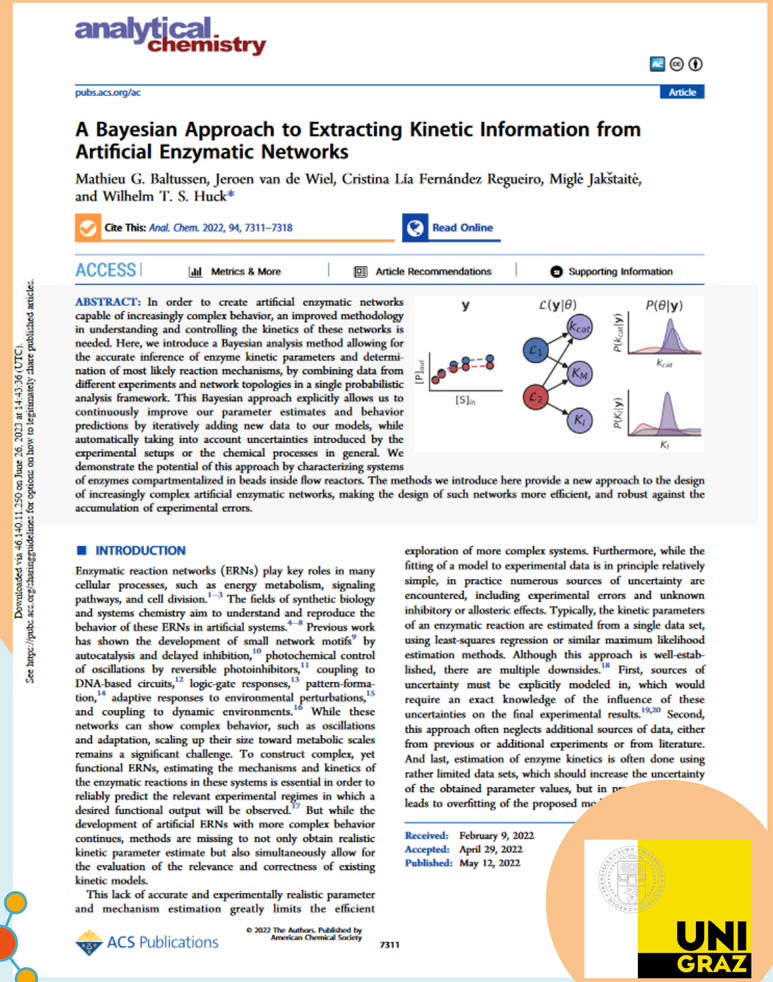

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A Bayesian Approach to Extracting Kinetic Information from Artificial Enzymatic Networks

Mathieu G. Baltussen, Jeroen van de Wiel, Cristina Lía Fernández Regueiro, Miglė Jakštaitė, and Wilhelm T. S. Huck*

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ABSTRACT: In order to create artificial enzymatic networks capable of increasingly complex behavior, an improved methodology in understanding and controlling the kinetics of these networks is needed. Here, we introduce a Bayesian analysis method allowing for the accurate inference of enzyme kinetic parameters and determination of most likely reaction mechanisms, by combining data from different experiments and network topologies in a single probabilistic analysis framework. This Bayesian approach explicitly allows us to continuously improve our parameter estimates and behavior predictions by iteratively adding new data to our models, while automatically taking into account uncertainties introduced by the experimental setups or the chemical processes in general. We demonstrate the potential of this approach by characterizing systems of enzymes compartmentalized in beads inside flow reactors. The methods we introduce here provide a new approach to the design of increasingly complex artificial enzymatic networks, making the design of such networks more efficient, and robust against the accumulation of experimental errors.

■ INTRODUCTION

Enzymatic reaction networks (ERNs) play key roles in many cellular processes, such as energy metabolism, signaling pathways, and cell division.[1−3] The fields of synthetic biology and systems chemistry aim to understand and reproduce the behavior of these ERNs in artificial systems.[4−8] Previous work has shown the development of small network motifs[9] by autocatalysis and delayed inhibition,[10] photochemical control of oscillations by reversible photoinhibitors,[11] coupling to DNA-based circuits,[12] logic-gate responses,[13] pattern-formation,[14] adaptive responses to environmental perturbations,[15] and coupling to dynamic environments.[16] While these networks can show complex behavior, such as oscillations and adaptation, scaling up their size toward metabolic scales remains a significant challenge. To construct complex, yet functional ERNs, estimating the mechanisms and kinetics of the enzymatic reactions in these systems is essential in order to reliably predict the relevant experimental regimes in which a desired functional output will be observed.[17] But while the development of artificial ERNs with more complex behavior continues, methods are missing to not only obtain realistic kinetic parameter estimate but also simultaneously allow for the evaluation of the relevance and correctness of existing kinetic models.

This lack of accurate and experimentally realistic parameter and mechanism estimation greatly limits the efficient exploration of more complex systems. Furthermore, while the fitting of a model to experimental data is in principle relatively simple, in practice numerous sources of uncertainty are encountered, including experimental errors and unknown inhibitory or allosteric effects. Typically, the kinetic parameters of an enzymatic reaction are estimated from a single data set, using least-squares regression or similar maximum likelihood estimation methods. Although this approach is well-established, there are multiple downsides.[18] First, sources of uncertainty must be explicitly modeled in, which would require an exact knowledge of the influence of these uncertainties on the final experimental results.[19,20] Second, this approach often neglects additional sources of data, either from previous or additional experiments or from literature. And last, estimation of enzyme kinetics is often done using rather limited data sets, which should increase the uncertainty of the obtained parameter values, but in pr... leads to overfitting of the proposed mo...

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From the authors

Using enzymes (nature's catalysts) can drastically simplify the process of making complex molecules. In our literature review, we show how this is particularly beneficial for pharmaceuticals as they often have a well-defined geometry and are expensive to produce.

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"Shortening Synthetic Routes to Small Molecule Active Pharmaceutical Ingredients Employing Biocatalytic Methods"

Stefan Simić, Erna Zukić, Luca Schmermund, Kurt Faber, Christoph K. Winkler, and Wolfgang Kroutil. Chem. Rev. 2022, 122, 1, 1052-1126;
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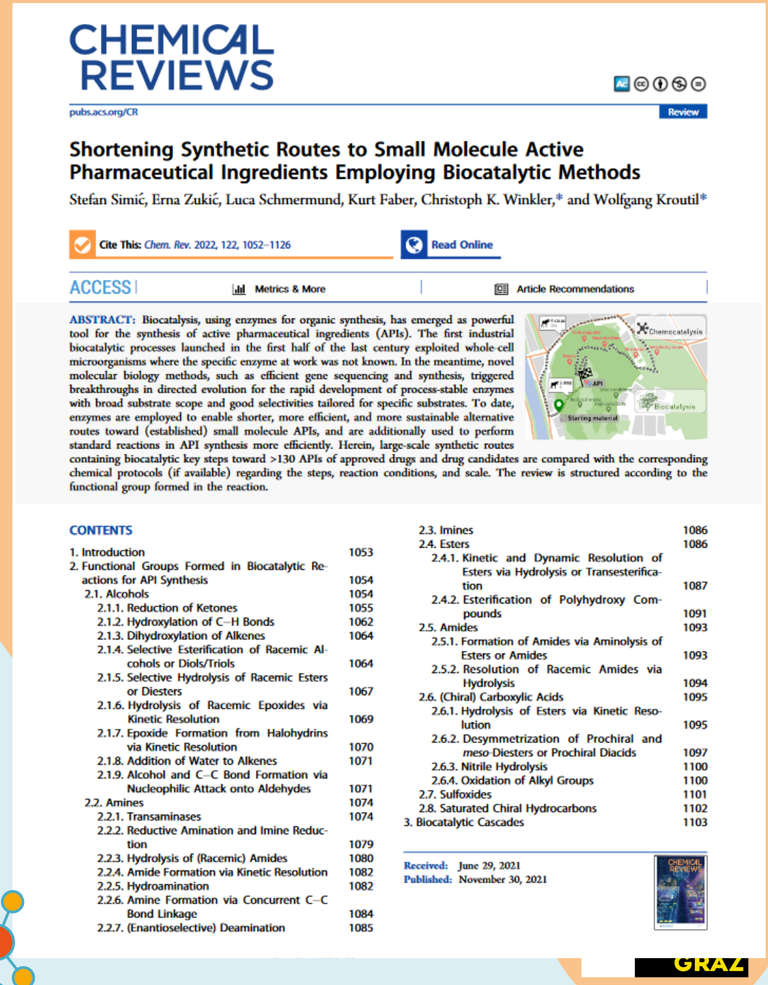
Doctoral researcher, Universität Graz, Biocatalysis Research Group



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Shortening Synthetic Routes to Small Molecule Active Pharmaceutical Ingredients Employing Biocatalytic Methods

Stefan Simić, Erna Zukić, Luca Schmermund, Kurt Faber, Christoph K. Winkler,* and Wolfgang Kroutil*

Cite This: *Chem. Rev.* 2022, 122, 1052−1126 | Read Online

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ABSTRACT: Biocatalysis, using enzymes for organic synthesis, has emerged as powerful tool for the synthesis of active pharmaceutical ingredients (APIs). The first industrial biocatalytic processes launched in the first half of the last century exploited whole-cell microorganisms where the specific enzyme at work was not known. In the meantime, novel molecular biology methods, such as efficient gene sequencing and synthesis, triggered breakthroughs in directed evolution for the rapid development of process-stable enzymes with broad substrate scope and good selectivities tailored for specific substrates. To date, enzymes are employed to enable shorter, more efficient, and more sustainable alternative routes toward (established) small molecule APIs, and are additionally used to perform standard reactions in API synthesis more efficiently. Herein, large-scale synthetic routes containing biocatalytic key steps toward >130 APIs of approved drugs and drug candidates are compared with the corresponding chemical protocols (if available) regarding the steps, reaction conditions, and scale. The review is structured according to the functional group formed in the reaction.

CONTENTS

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From the authors

We demonstrate that the formation of well-defined structures by double-stranded DNA-peptide conjugates is restricted to a specific range of environmental conditions and that precise DNA hybridization, satisfying the interaction interfaces, is a crucial factor in this process.

13

"Dynamic exchange controls the assembly structure of nucleic-acid-peptide chimeras"

Hava Sadihov-Hanoch, Anil Kumar Bandela, Agata Chotera-Ouda, Oshrat Ben David, Rivka Cohen-Luria, David G. Lynn and Gonen Ashkenasy. Soft Matter 2023, 19, 3940-3945.
DOI: https://doi.org/10.1039/D2SM01528E

GONEN ASHKENASY
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Dynamic exchange controls the assembly structure of nucleic-acid-peptide chimeras†

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Hava Sadihov-Hanoch,[a] Anil Kumar Bandela,[a] Agata Chotera-Ouda,[a] Oshrat Ben David,[a] Rivka Cohen-Luria,[a] David G. Lynn[b] and Gonen Ashkenasy[*a]

Author affiliations

Abstract

Recent attempts to develop the next generation of functional biomaterials focus on systems chemistry approaches exploiting dynamic networks of hybrid molecules. This task is often found challenging, but we herein present ways for profiting from the multiple interaction interfaces forming Nucleic-acid-Peptide assemblies and tuning their formation. We demonstrate that the formation of well-defined structures by double-stranded DNA-peptide conjugates (dsCon) is restricted to a specific range of environmental conditions and that precise DNA hybridization, satisfying the interaction interfaces, is a crucial factor in this process. We further reveal the impact of external stimuli, such as competing free DNA elements or salt additives, which initiate dynamic interconversions, resulting in hybrid structures exhibiting spherical and fibrillar domains or a mixture of spherical and fibrillar particles. This extensive analysis of the co-assembly systems chemistry offers new insights into prebiotic hybrid assemblies that may now facilitate the design of new functional materials. We discuss the implications of these findings for the emergence of function in synthetic materials and during early chemical evolution.

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From the authors

What I really enjoyed during this project is how we build on the detailed knowledge of our peptide catalysts to develop a novel transformation which gives access to versatile building blocks.

14

"Organocatalytic Synthesis of Triflones Bearing Two Non-Adjacent Stereogenic Centers"

Alena Budinská and Helma Wennemers.
Angew. Chem. Int. Ed. 2023, e202300537
DOI: Angew. Chem. Int. Ed. 2023, e202300537

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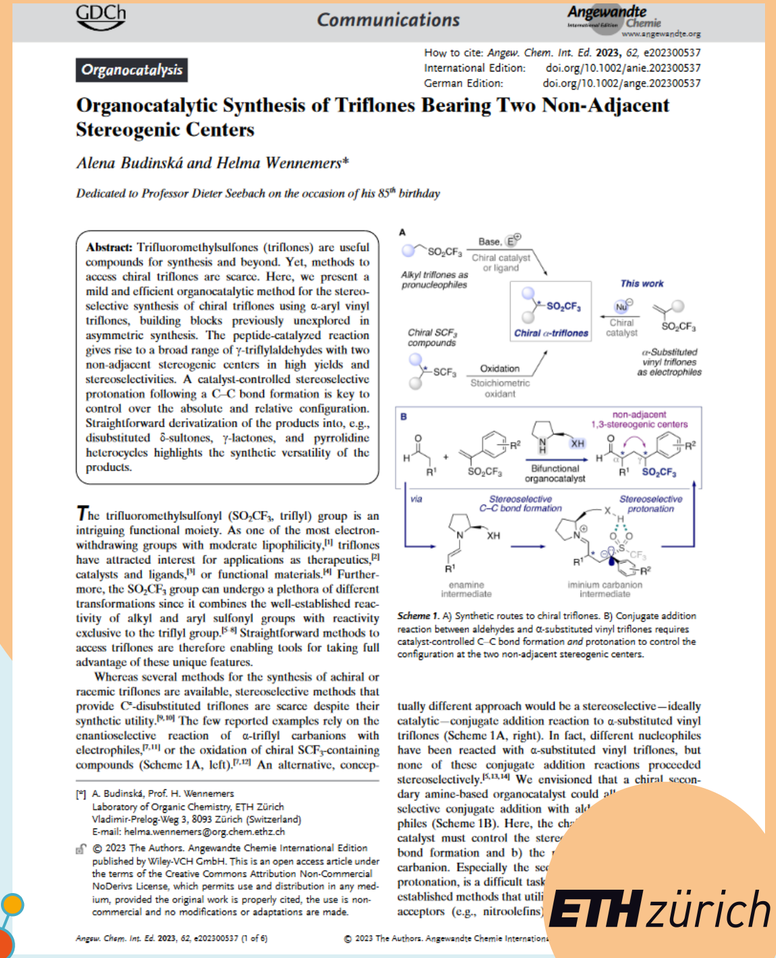

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Organocatalysis

Organocatalytic Synthesis of Triflones Bearing Two Non-Adjacent Stereogenic Centers

*Alena Budinská and Helma Wennemers**

Dedicated to Professor Dieter Seebach on the occasion of his 85th birthday

Abstract: Trifluoromethylsulfones (triflones) are useful compounds for synthesis and beyond. Yet, methods to access chiral triflones are scarce. Here, we present a mild and efficient organocatalytic method for the stereoselective synthesis of chiral triflones using α-aryl vinyl triflones, building blocks previously unexplored in asymmetric synthesis. The peptide-catalyzed reaction gives rise to a broad range of γ-triflylaldehydes with two non-adjacent stereogenic centers in high yields and stereoselectivities. A catalyst-controlled stereoselective protonation following a C–C bond formation is key to control over the absolute and relative configuration. Straightforward derivatization of the products into, e.g., disubstituted δ-sultones, γ-lactones, and pyrrolidine heterocycles highlights the synthetic versatility of the products.

Scheme 1. A) Synthetic routes to chiral triflones. B) Conjugate addition reaction between aldehydes and α-substituted vinyl triflones requires catalyst-controlled C–C bond formation *and* protonation to control the configuration at the two non-adjacent stereogenic centers.

The trifluoromethylsulfonyl (SO_2CF_3, triflyl) group is an intriguing functional moiety. As one of the most electron-withdrawing groups with moderate lipophilicity,[1] triflones have attracted interest for applications as therapeutics,[2] catalysts and ligands,[3] or functional materials.[4] Furthermore, the SO_2CF_3 group can undergo a plethora of different transformations since it combines the well-established reactivity of alkyl and aryl sulfonyl groups with reactivity exclusive to the triflyl group.[5–8] Straightforward methods to access triflones are therefore enabling tools for taking full advantage of these unique features.

Whereas several methods for the synthesis of achiral or racemic triflones are available, stereoselective methods that provide C^α-disubstituted triflones are scarce despite their synthetic utility.[9,10] The few reported examples rely on the enantioselective reaction of α-triflyl carbanions with electrophiles,[7,11] or the oxidation of chiral SCF_3-containing compounds (Scheme 1A, left).[7,12] An alternative, conceptually different approach would be a stereoselective—ideally catalytic—conjugate addition reaction to α-substituted vinyl triflones (Scheme 1A, right). In fact, different nucleophiles have been reacted with α-substituted vinyl triflones, but none of these conjugate addition reactions proceeded stereoselectively.[7,13,14] We envisioned that a chiral secondary amine-based organocatalyst could al… selective conjugate addition with al… philes (Scheme 1B). Here, the ch… catalyst must control the stere… bond formation and b) the … carbanion. Especially the se… protonation, is a difficult task… established methods that utili… acceptors (e.g., nitroolefins…

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From the authors

Our results provide basic insights into the principles of catalysis and oligomerization which are key processes for the evolution of life. They are the first step in creating molecular assembly lines for the construction of complex molecules from simple individual components – a goal at the heart of CLASSY.

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"Catalytic length-controlled oligomerization with synthetic programmable templates"

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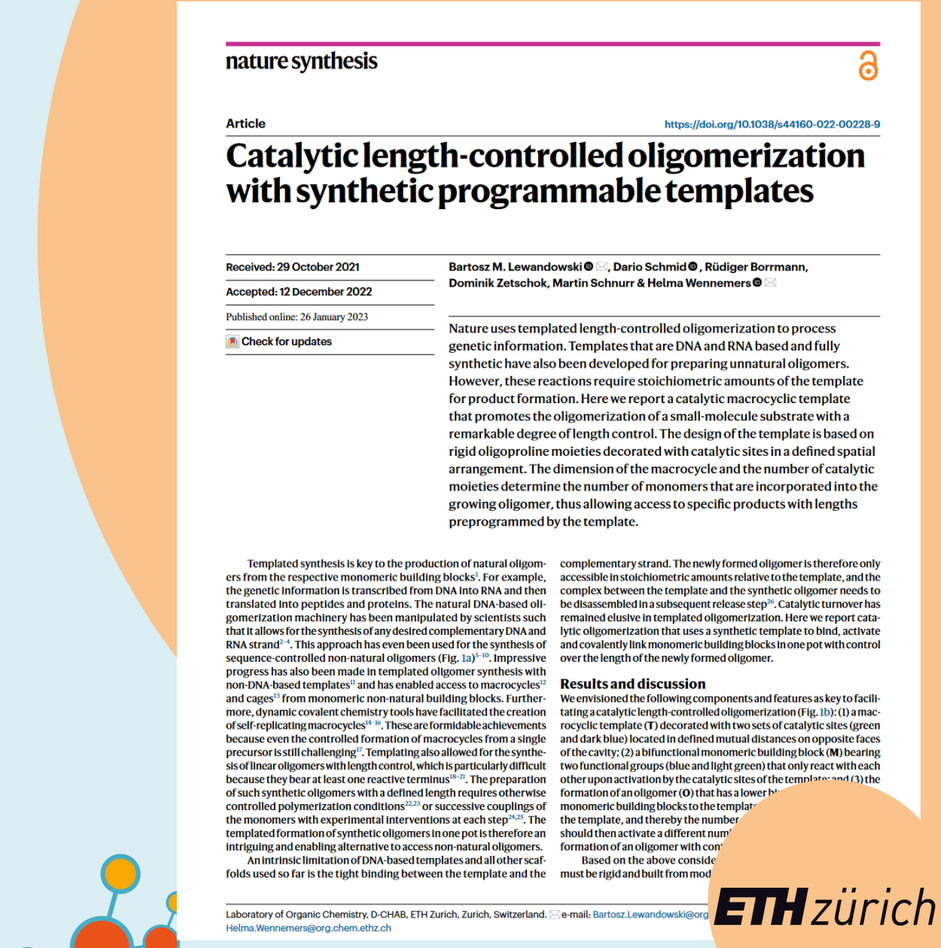

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Catalytic length-controlled oligomerization with synthetic programmable templates

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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 b… monomeric building blocks to the templat… the template, and thereby the number… should then activate a different num… formation of an oligomer with con…

Based on the above conside… must be rigid and built from mod…

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From the authors

This work shows the importance of self-assembly in the control of aqueous peptide-based catalysts, and how complementary nucleobases can be used to fine-tune their supramolecular structure and catalytic activity, improving both the conversion and diastereoselectivity.

16

"Modifying the catalytic activity of lipopeptide assemblies with nucleobases"

Sonia Vela-Gallego, Bartosz Lewandowski, Jasper Möhler, Alonso Puente, David Gil-Cantero, Helma Wennemers, Andrés de la Escosura

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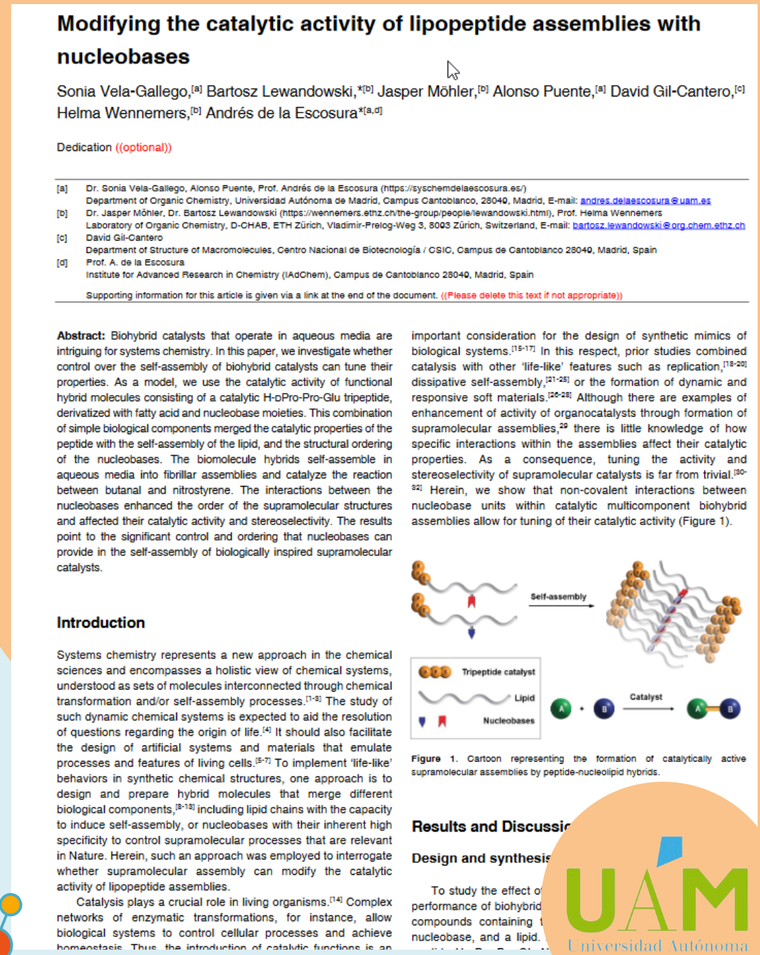

Modifying the catalytic activity of lipopeptide assemblies with nucleobases

Sonia Vela-Gallego,[a] Bartosz Lewandowski,*[b] Jasper Möhler,[b] Alonso Puente,[a] David Gil-Cantero,[c] Helma Wennemers,[b] Andrés de la Escosura*[a,d]

Dedication ((optional))

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Abstract: Biohybrid catalysts that operate in aqueous media are intriguing for systems chemistry. In this paper, we investigate whether control over the self-assembly of biohybrid catalysts can tune their properties. As a model, we use the catalytic activity of functional hybrid molecules consisting of a catalytic H-DPro-Pro-Glu tripeptide, derivatized with fatty acid and nucleobase moieties. This combination of simple biological components merged the catalytic properties of the peptide with the self-assembly of the lipid, and the structural ordering of the nucleobases. The biomolecule hybrids self-assemble in aqueous media into fibrillar assemblies and catalyze the reaction between butanal and nitrostyrene. The interactions between the nucleobases enhanced the order of the supramolecular structures and affected their catalytic activity and stereoselectivity. The results point to the significant control and ordering that nucleobases can provide in the self-assembly of biologically inspired supramolecular catalysts.

Introduction

Systems chemistry represents a new approach in the chemical sciences and encompasses a holistic view of chemical systems, understood as sets of molecules interconnected through chemical transformation and/or self-assembly processes.[1-3] The study of such dynamic chemical systems is expected to aid the resolution of questions regarding the origin of life.[4] It should also facilitate the design of artificial systems and materials that emulate processes and features of living cells.[5-7] To implement 'life-like' behaviors in synthetic chemical structures, one approach is to design and prepare hybrid molecules that merge different biological components,[8-12] including lipid chains with the capacity to induce self-assembly, or nucleobases with their inherent high specificity to control supramolecular processes that are relevant in Nature. Herein, such an approach was employed to interrogate whether supramolecular assembly can modify the catalytic activity of lipopeptide assemblies.

Catalysis plays a crucial role in living organisms.[14] Complex networks of enzymatic transformations, for instance, allow biological systems to control cellular processes and achieve homeostasis. Thus, the introduction of catalytic functions is an important consideration for the design of synthetic mimics of biological systems.[15-17] In this respect, prior studies combined catalysis with other 'life-like' features such as replication,[18-20] dissipative self-assembly,[21-25] or the formation of dynamic and responsive soft materials.[26-28] Although there are examples of enhancement of activity of organocatalysts through formation of supramolecular assemblies,[29] there is little knowledge of how specific interactions within the assemblies affect their catalytic properties. As a consequence, tuning the activity and stereoselectivity of supramolecular catalysts is far from trivial.[30-32] Herein, we show that non-covalent interactions between nucleobase units within catalytic multicomponent biohybrid assemblies allow for tuning of their catalytic activity (Figure 1).

Figure 1. Cartoon representing the formation of catalytically active supramolecular assemblies by peptide-nucleolipid hybrids.

Results and Discussi

Design and synthesis

To study the effect o
performance of biohybrid
compounds containing t
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From the authors

This review reflects about the high interconnection existing between the main prebiotic synthetic routes, pointing out how common intermediates and catalytic cycles connecting them would be critical to establish self-organized and dissipative networks as constituents of primitive minimal metabolisms.

17

"The protometabolic nature of prebiotic chemistry"

Sonia Vela-Gallego, Bartosz Lewandowski, Jasper Möhler, Alonso Puente, David Gil-Cantero, Helma Wennemers, Andrés de la Escosura

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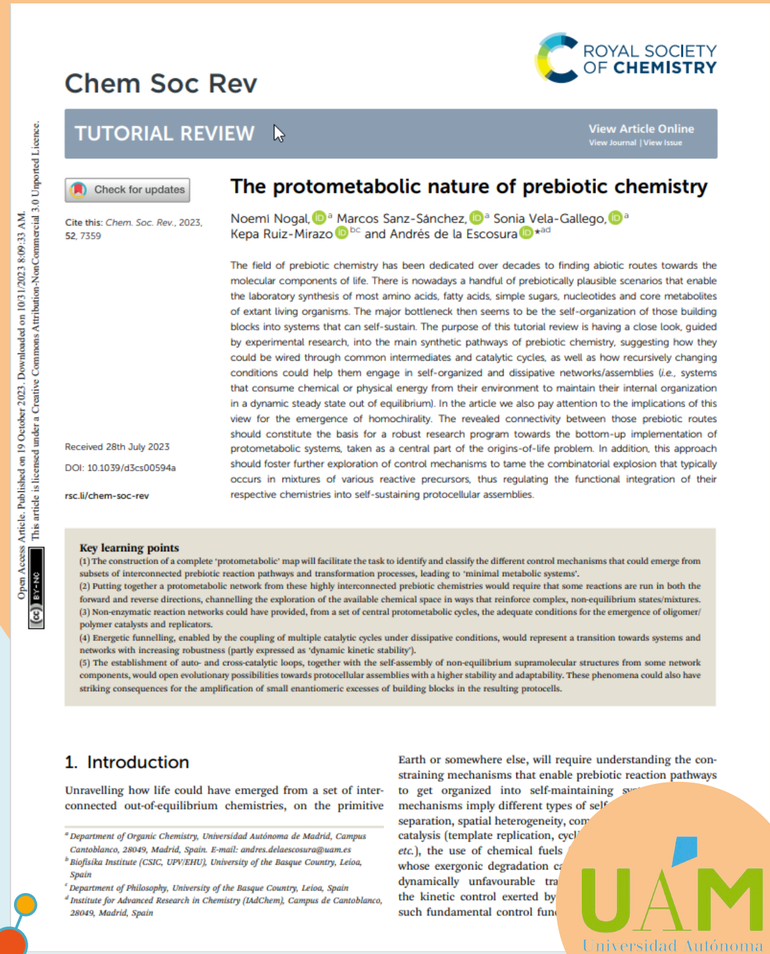

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The protometabolic nature of prebiotic chemistry

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Noemi Nogal, Marcos Sanz-Sánchez, Sonia Vela-Gallego, Kepa Ruiz-Mirazo and Andrés de la Escosura

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The field of prebiotic chemistry has been dedicated over decades to finding abiotic routes towards the molecular components of life. There is nowadays a handful of prebiotically plausible scenarios that enable the laboratory synthesis of most amino acids, fatty acids, simple sugars, nucleotides and core metabolites of extant living organisms. The major bottleneck then seems to be the self-organization of those building blocks into systems that can self-sustain. The purpose of this tutorial review is having a close look, guided by experimental research, into the main synthetic pathways of prebiotic chemistry, suggesting how they could be wired through common intermediates and catalytic cycles, as well as how recursively changing conditions could help them engage in self-organized and dissipative networks/assemblies (*i.e.*, systems that consume chemical or physical energy from their environment to maintain their internal organization in a dynamic steady state out of equilibrium). In the article we also pay attention to the implications of this view for the emergence of homochirality. The revealed connectivity between those prebiotic routes should constitute the basis for a robust research program towards the bottom-up implementation of protometabolic systems, taken as a central part of the origins-of-life problem. In addition, this approach should foster further exploration of control mechanisms to tame the combinatorial explosion that typically occurs in mixtures of various reactive precursors, thus regulating the functional integration of their respective chemistries into self-sustaining protocellular assemblies.

Key learning points

(1) The construction of a complete 'protometabolic' map will facilitate the task to identify and classify the different control mechanisms that could emerge from subsets of interconnected prebiotic reaction pathways and transformation processes, leading to 'minimal metabolic systems'.
(2) Putting together a protometabolic network from these highly interconnected prebiotic chemistries would require that some reactions are run in both the forward and reverse directions, channelling the exploration of the available chemical space in ways that reinforce complex, non-equilibrium states/mixtures.
(3) Non-enzymatic reaction networks could have provided, from a set of central protometabolic cycles, the adequate conditions for the emergence of oligomer/polymer catalysts and replicators.
(4) Energetic funnelling, enabled by the coupling of multiple catalytic cycles under dissipative conditions, would represent a transition towards systems and networks with increasing robustness (partly expressed as 'dynamic kinetic stability').
(5) The establishment of auto- and cross-catalytic loops, together with the self-assembly of non-equilibrium supramolecular structures from some network components, would open evolutionary possibilities towards protocellular assemblies with a higher stability and adaptability. These phenomena could also have striking consequences for the amplification of small enantiomeric excesses of building blocks in the resulting protocells.

1. Introduction

Unravelling how life could have emerged from a set of interconnected out-of-equilibrium chemistries, on the primitive Earth or somewhere else, will require understanding the constraining mechanisms that enable prebiotic reaction pathways to get organized into self-maintaining s... mechanisms imply different types of sel... separation, spatial heterogeneity, com... catalysis (template replication, cycl... *etc.*), the use of chemical fuels ... whose exergonic degradation c... dynamically unfavourable tra... the kinetic control exerted by ... such fundamental control fun...

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From the authors

Here, we show that catalyst deactivation can be overcome by catalysts that bear an intramolecular acid for protonation and release of the alkylated catalyst through ß-elimination of the nitroolefin.

18

"Overcoming Deactivation of Amine-based Catalysts: Access to Fluoroalkylated γ-Nitroaldehydes"

Martin Schnurr, Jonas W. Rackl and Helma Wennemers.
DOI: https://doi.org/10.1039/d2sc02044k

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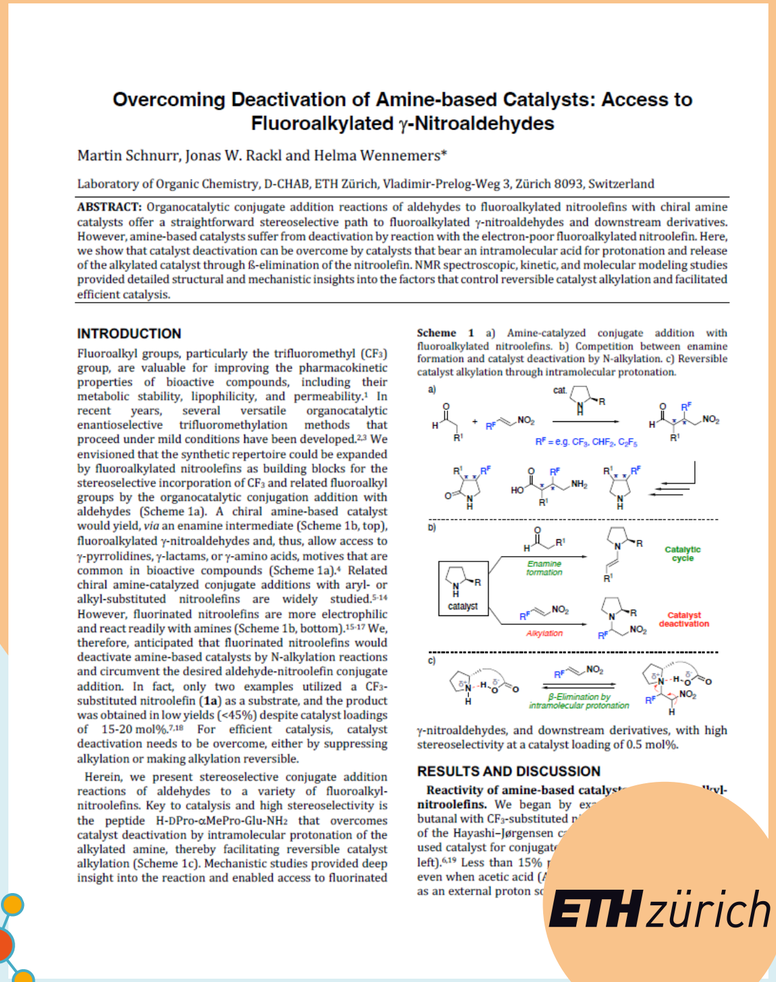

Overcoming Deactivation of Amine-based Catalysts: Access to Fluoroalkylated γ-Nitroaldehydes

Martin Schnurr, Jonas W. Rackl and Helma Wennemers*

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ABSTRACT: Organocatalytic conjugate addition reactions of aldehydes to fluoroalkylated nitroolefins with chiral amine catalysts offer a straightforward stereoselective path to fluoroalkylated γ-nitroaldehydes and downstream derivatives. However, amine-based catalysts suffer from deactivation by reaction with the electron-poor fluoroalkylated nitroolefin. Here, we show that catalyst deactivation can be overcome by catalysts that bear an intramolecular acid for protonation and release of the alkylated catalyst through ß-elimination of the nitroolefin. NMR spectroscopic, kinetic, and molecular modeling studies provided detailed structural and mechanistic insights into the factors that control reversible catalyst alkylation and facilitated efficient catalysis.

INTRODUCTION

Fluoroalkyl groups, particularly the trifluoromethyl (CF_3) group, are valuable for improving the pharmacokinetic properties of bioactive compounds, including their metabolic stability, lipophilicity, and permeability.[1] In recent years, several versatile organocatalytic enantioselective trifluoromethylation methods that proceed under mild conditions have been developed.[2,3] We envisioned that the synthetic repertoire could be expanded by fluoroalkylated nitroolefins as building blocks for the stereoselective incorporation of CF_3 and related fluoroalkyl groups by the organocatalytic conjugation addition with aldehydes (Scheme 1a). A chiral amine-based catalyst would yield, *via* an enamine intermediate (Scheme 1b, top), fluoroalkylated γ-nitroaldehydes and, thus, allow access to γ-pyrrolidines, γ-lactams, or γ-amino acids, motives that are common in bioactive compounds (Scheme 1a).[4] Related chiral amine-catalyzed conjugate additions with aryl- or alkyl-substituted nitroolefins are widely studied.[5-14] However, fluorinated nitroolefins are more electrophilic and react readily with amines (Scheme 1b, bottom).[15-17] We, therefore, anticipated that fluorinated nitroolefins would deactivate amine-based catalysts by N-alkylation reactions and circumvent the desired aldehyde-nitroolefin conjugate addition. In fact, only two examples utilized a CF_3-substituted nitroolefin (**1a**) as a substrate, and the product was obtained in low yields (<45%) despite catalyst loadings of 15-20 mol%.[7,18] For efficient catalysis, catalyst deactivation needs to be overcome, either by suppressing alkylation or making alkylation reversible.

Herein, we present stereoselective conjugate addition reactions of aldehydes to a variety of fluoroalkyl-nitroolefins. Key to catalysis and high stereoselectivity is the peptide H-DPro-αMePro-Glu-NH_2 that overcomes catalyst deactivation by intramolecular protonation of the alkylated amine, thereby facilitating reversible catalyst alkylation (Scheme 1c). Mechanistic studies provided deep insight into the reaction and enabled access to fluorinated

Scheme 1 a) Amine-catalyzed conjugate addition with fluoroalkylated nitroolefins. b) Competition between enamine formation and catalyst deactivation by N-alkylation. c) Reversible catalyst alkylation through intramolecular protonation.

γ-nitroaldehydes, and downstream derivatives, with high stereoselectivity at a catalyst loading of 0.5 mol%.

RESULTS AND DISCUSSION

Reactivity of amine-based catalyst… …lkyl-nitroolefins. We began by ex… butanal with CF_3-substituted n… of the Hayashi–Jørgensen c… used catalyst for conjugat… left).[6,19] Less than 15% … even when acetic acid (A… as an external proton so…

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