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Swiss Science Concentrates

A CHIMIA Column

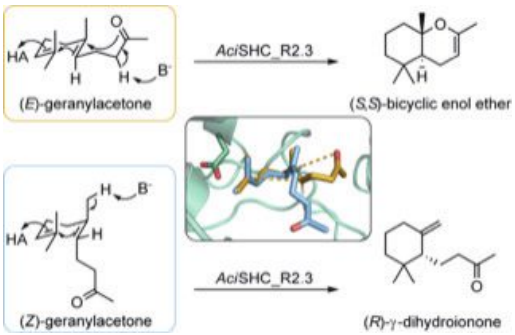
Short Abstracts of Interesting Recent Publications of Swiss Origin

Asymmetric cation-olefin monocyclization by engineered squalene-hopene cyclases

Michael Eichenberger, Sean Hüppi, David Patsch, Natalie Aeberli, Raphael Berweger, Sandro Dossenbach, Eric Eichhorn, Felix Flachsmann, Lucas Hortencio, Francis Voirol, Sabine Vollenweider, Uwe T. Bornscheuer, Rebecca Buller,* *Angew. Chem. Int. Ed.* **2021**, *60*, 26080–26086. https://doi.org/10.1002/anie.202108037
Zurich University of Applied Sciences; Delft University of Technology; Greifswald University; Givaudan Schweiz AG & International SA

Squalene-hopene cyclases (SHCs) hold great potential for the industrial synthesis of enantiopure cyclic terpenoids. While these enzymes were known to be strictly (*S*)-enantioselective, the authors synthetised (*R*)-γ-dihydroionone from (*Z*)-geranylacetone with 79% yield based on protein engineering of a novel SHC homolog (*Aci*SHC). Moreover, the *Aci*SHC variants exhibited exquisite isomeric selectivity, with the (*Z*)- and the (*E*)-geranylacetone isomers being converted to the desired (*R*)-γ-dihydroionone and the (*S*,*S*)-bicyclic ether, respectively. Harnessing knowledge from the stereodivergent and enantioselective transformations, the complementary (*S*)-γ-dihydroionone was ultimately obtained by choosing an appropriate SHC-substrate pair. Overall, this study expands the scope of accessible monocyclic terpenoids by highlighting the possibility to fine-tune the absolute configuration of the cyclized products and to control the polycyclization cascade through substrate engineering.

Authors' comments:
"Using the capability of engineered squalene-hopene cyclases to discriminate between geometric isomers of the substrate, this work demonstrates chemoenzymatic routes to the optical antipodes of a commercially relevant cyclic monoterpenoid."

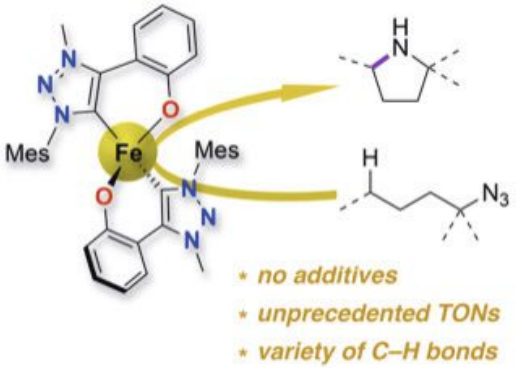


An iron-mesoionic carbene complex for catalytic intramolecular C–H amination utilizing organic azides

Wowa Stroek, Martin Keilwerth, Daniel M. Pividori, Karsten Meyer, Martin Albrecht,* *J. Am. Chem. Soc.* **2021**, *143*, 20157–20165. https://doi.org/10.1021/jacs.1c07378
University of Bern

Traditionally the synthesis of N-heterocycles is very environmental demanding since large amounts of waste and toxic compounds are generated. In this article the authors report a greener alternative through the direct intramolecular C–H amination, using an iron-mesoionic carbene complex. Remarkably, this iron-based complex does not need any additives to be active such as Boc_2O or pyridine. The achieved turnover number of 7600 is one order of magnitude higher than the previous works, increasing so the overall catalytic efficiency. The applicability of the system was tested on different substrates achieving good yields and functional group tolerance upon the intramolecular C–H amination. In line with the kinetic studies the authors proposed a new mechanism compared to other systems, in which the activation of the catalyst goes through a dimeric iron species.

Authors' comments:
"It was rewarding to see that appropriate stabilization of the carbene bonding to iron created a highly robust catalytic system that remains active for days. This strategy may enable the catalytic activation of other strong bonds."



Prepared by Lucia Robustini, Valentina Marchini, Lauriane Pillet, David Lim, and Francesca Paradisi*
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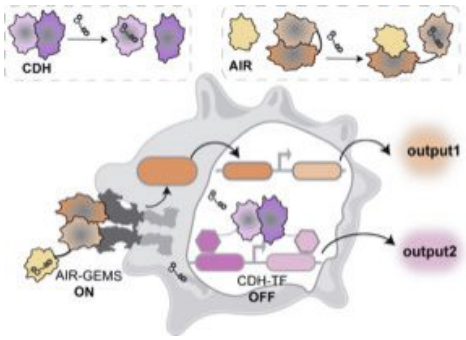
A rational blueprint for the design of chemically-controlled protein switches

Sailan Shui, Pablo Gainza, Leo Scheller, Che Yang, Yoichi Kurumida, Stéphane Rosset, Sandrine Georgeon, Raphaël B. Di Roberto, Rocío Castellanos-Rueda, Sai T. Reddy, Bruno E. Correia,* *Nat. Commun.* **2021**, *12*, 5754. https://doi.org/10.1038/s41467-021-25735-9
École Polytechnique Fédérale de Lausanne; Swiss Institute of Bioinformatics, Lausanne; ETH Zürich; Tokyo Institute of Technology, Japan

This work expanded the panel of small-molecule controllable protein switches, available to control the assembly or disassembly of protein complexes for synthetic cellular activities. A structure-based and computational protein design strategy has been developed to repurpose drug-inhibited protein-protein interactions as OFF- and ON- switches. Three new chemically disruptable heterodimers (CDH) were designed and used to regulate cellular responses. Furthermore, the CDHs were repurposed to create ON switches, named as *activation by inhibitor release switch* (AIR), by converting the CDHs into a multi-domain architecture that incorporates a rationally designed insensitive drug receptor protein. CDHs and AIRs showed excellent performance as drug responsive switches to control combinations of synthetic circuits in mammalian cells. This approach effectively provides a blueprint to develop novel small-molecule switches.

Authors' comments:
"This work presents rationally designed chemically responsive OFF- and ON-switches controlled by preclinical or clinically validated drugs. These protein switches are also useful tools in synthetic biology and cancer immunotherapy."



Protamine/heparin optical nanosensors based on solvatochromism

Yoshiki Soda, Kye J. Robinson, Robin Nussbaum, Eric Bakker,* *Chem. Sci.*, **2021**, *12*, 15596–15602. https://doi.org/10.1039/d1sc04930e
University of Geneva, Geneva, Switzerland

Until now, the use of optical nanosensors to detect polyanions, including protamine and heparin, has been limited to the use of ion-exchange reactions with an analyte and an optical transducer. Unfortunately, as a consequence of reduced selectivity of available ionophores for polyions, the method incurs interference when faced with complex sample matrices. In the case of serum, plasma or blood, there are currently no optical polyion nanosensors producing acceptable standards of analysis. However, we have created a new type of nanosensor based on our discovery of a 'hyper-polarizing lipophilic phase' in which dinonylnaphthalenesulfonate ($DNNS^-$) polarizes a solvatochromic dye, more successfully than in an aqueous environment. The findings show that the apparent polarity of the organic phase is only modulated when $DNSS^-$ binds to large polyions like protamine. This differs to singly charged ions that lack cooperative binding and significant polarization. The new mechanism permits signal transduction, improved sensitivity and selectivity.

Authors' comments:
"This research shows how puzzling findings can turn out to have unexpected benefits. The signal change was opposite to the one we expected, suggesting that the dye finds a *less* polar environment as protamine is provided to solution. The final result is very beautiful."