doi:10.2533/chimia.2024.261 Chimia 78 (2024) 261–262

Swiss Science Concentrates

A CHIMIA Column

Short Abstracts of Interesting Recent Publications of Swiss Origin

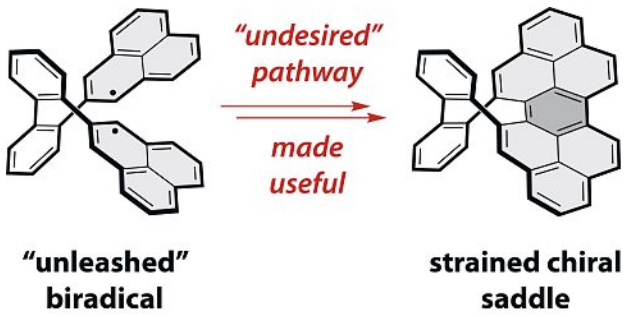
π-Radical Cascade to a Chiral Saddle-Shaped Peropyrene

Annika Bernhardt, Daniel Čavlović, Maximilian Mayländer, Olivier Blacque, Carlos M. Cruz*, Sabine Richert*, and Michal Juríček*

Angew. Chem. Int. Ed. **2024**, e202318254, https://doi.org/10.1002/anie.202318254
University of Granada, University of Freiburg, University of Zurich

This study challenges the conventional perception of open-shell molecular graphene fragment reactions as undesired decomposition processes, showcasing their potential as synthetic tools for the costruction of complex nanostructures. The oxidative dimerization of phenalenyl to peropyrene serves as an example, demonstrating the formation of multiple bonds and a ring in a single step. The investigation explores the 'undesired' reaction of phenalenyl to introduce strain, leading to the synthesis of nonplanar polycyclic aromatic hydrocarbon. A biradical system with two phenalenyl units linked *via* a biphenylene backbone was designed for this purpose. Intramolecular cascade reactions facilitated the formation of a helically twisted saddle-shaped product, involving key transformations like ring-closure and ring-fusion. Single-crystal X-ray diffraction confirmed the product's negative curvature induced by an eight-membered ring, while the resolution of enantiomers revealed circularly polarized luminescence and high configurational stability, validating the success of the synthetic approach.

***Authors' comments*:**
"To demonstrate the usefulness of 'undesired' reaction pathways of open-shell graphene fragments, we make use of oxidative dimerization of phenalenyl to peropyrene to build up strain and induce negative curvature."



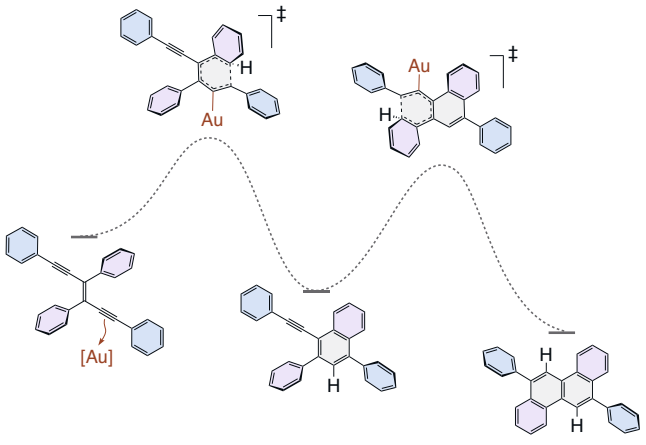
Dramatic Acceleration of the Hopf Cyclization on Gold(111): From Enediynes to Peri-Fused Diindenochrysene Graphene Nanoribbons

Chenxiao Zhao, Dayanni D. Bhagwandin, Wangwei Xu, Pascal Ruffieux, Saeed I. Khan, Carlo A. Pignedoli*, Roman Fasel*, and Yves Rubin*

J. Am. Chem. Soc. **2024**, *146*, 2474, https://10.1021/jacs.3c10144
Swiss Federal Laboratories for Material Science and Technology Empa, Dübendorf, Switzerland; University of Bern, Switzerland; University of California, Los Angeles, USA.

In 1969, Hopf *et al.* documented the high-temperature 6π-electrocyclization of *cis*-hexa-1,3-diene-5-yne to benzene, but subsequent investigations faced limitations due to the formidable reaction barrier. This study reveals an almost 50% reduction in the reaction barrier for the Hopf cyclization when conducted on an Au(111) surface. Scanning tunneling microscopy (STM) and noncontact atomic force microscopy (nc-AFM) were employed to monitor the cyclization: Enediyne undergoes two quantitative Hopf cyclizations, first to a naphthalene derivative and finally to a chrysene derivative, revealing the crucial involvement of a gold atom from the Au(111) surface in lowering the reaction barrier. Combining Hopf cyclization with Ullmann-like reactions extends implications to the synthesis of diverse graphene nanoribbons, presenting a novel route for nanographene structures on Au(111).

***Authors' comments*:**
"This study is the result of a symbiotic collaboration between our two research groups, where each author's contribution proved critical in elucidating the gold surface's beneficial influence on the Hopf cyclization reaction. This pivotal finding represents a significant advancement in our quest to diversify methods for graphene nanoribbon syntheses, ultimately paving the way for nanotransistor development."



Prepared by Cesare Berton, Patrick A. Cieslik, Fan Liu, Stanislav Prytuliak, Simon Klinger, Jonas Genz, Eda Nisli, Deborah Bäcker, Henrik Braband and Jason P. Holland*
Do you want your article to appear in the SWISS SCIENCE CONCENTRATES highlight?
Please contact jason.holland@chem.uzh.ch

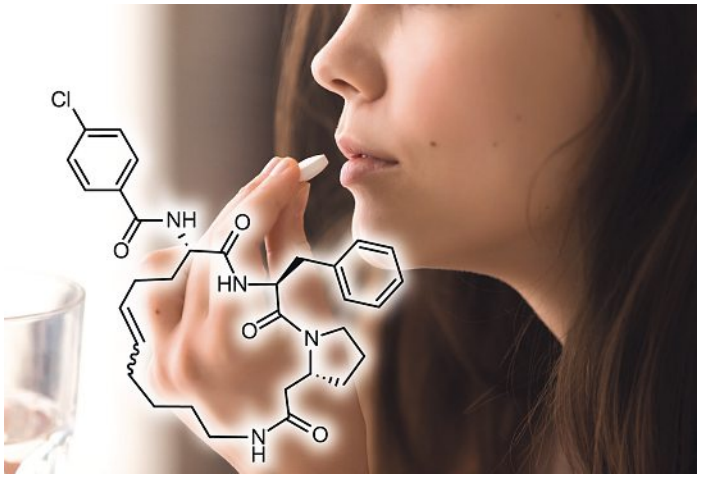
De Novo Development of Small Cyclic Peptides that are Orally Bioavailable

Manuel L. Merz, Sevan Habeshian, Bo Li, Jean-Alexandre G. L. David, Alexander L. Nielsen, Xinjian Ji, Khaled Il Khwildy, Maury M. Duany Benitez, Phoukham Phothirath, and Christian Heinis*

Nat. Chem. Biol., **2023**, https://doi.org/10.1038/s41589-023-01496-y
EPFL

Cyclic peptides offer potential in targeting challenging diseases, but their oral application is limited due to rapid digestion and/or low absorption. In this study, authors introduce a synthesis and screening method that combines sequential cyclization and peptide acylation, enabling simultaneous activity and permeability assessment. As a proof of concept, 8,448 cyclic peptides were synthesized and screened against thrombin. This approach facilitated iterative library synthesis, resulting in nanomolar affinities, high stability, and up to 18% oral bioavailability in rats. This method holds promise in unlocking peptides' therapeutic potential, addressing unmet medical needs.

Authors' comments:
"We were very excited to see that a *de novo* developed cyclic peptide can be orally applied. We now use the same technology for developing cyclic peptides to challenging targets such as protein-protein interactions and hope that these efforts will lead to the development of orally available cyclic peptide therapeutics."



How Cycloalkane Fusion Enhances the Cycloaddition Reactivity of Dibenzocyclooctynes

Dennis Svatunek*, Anton Murnauer, Zhuoting Tan, K. N. Houk, and Kathrin Lang*

Chem. Sci., **2024**, Advance Article, https://doi.org/10.1039/D3SC05789E

[a]Department of Chemistry and Biochemistry, University of California, USA; [b]Institute of Applied Synthetic Chemistry, TU Wien, Getreidemarkt 9, 1060 Vienna, AustriaHoffmann–La Roche, Ltd., Basel, Switzerland; [c]Department of Chemistry and Applied Biosciences, ETH Zurich, CH-8093 Zurich, Switzerland

Dibenzoannulated cyclooctynes have gained significance in bioorthogonal reactions, particularly in strain-promoted 1,3-dipolar cycloadditions when paired with azides. Despite their utility, these compounds traditionally exhibit low reactivity with 3,6-disubstituted tetrazines in inverse electron-demand Diels–Alder cycloadditions. Recently, a derivative, namely dibenzoannulated bicyclo[6.1.0]nonyne (DMBO), incorporating a cyclopropane fused to the cyclooctyne core, demonstrated unexpected reactivity towards tetrazines. To elucidate this unique behavior, density functional theory calculations were employed. The analysis unveiled a tubular structure in the transition state, resulting in a significantly reduced activation barrier compared to non-cyclopropane-fused analogs. Interestingly, this transition state geometry, favorable for tetrazine reactivity, was consistent across various cycloalkanes fused to the cyclooctyne core, albeit with higher activation barriers for larger ring sizes. This unconventional conformation, energetically unfavorable for typical dibenzoannulated cyclooctynes, allows tetrazines and azides to approach DMBO from the face rather than the edge, representing a previously unobserved trajectory for this class of activated dieno- and dipolarophiles.

Authors' comments:
"Together with Dennis Svatunek and Ken Houk we investigated the distinct reactivity of cycloalkane-fused dibenzocyclooctynes in cycloaddition reactions, both computationally and experimentally. The new insights on the transition state geometries and reaction trajectories may pave the way for the development of novel bioorthogonal probes."