



Swiss Science Concentrates

A CHIMIA Column

Short Abstracts of Interesting Recent Publications of Swiss Origin

Using Machine Learning to Predict the Antibacterial Activity of Ruthenium Complexes

Markus Orsi, Boon Shing Loh, Cheng Weng, Wee Han Ang*, and Angelo Frei*

Angew. Chem. Int. Ed., **2024**, *10*, e202317901.

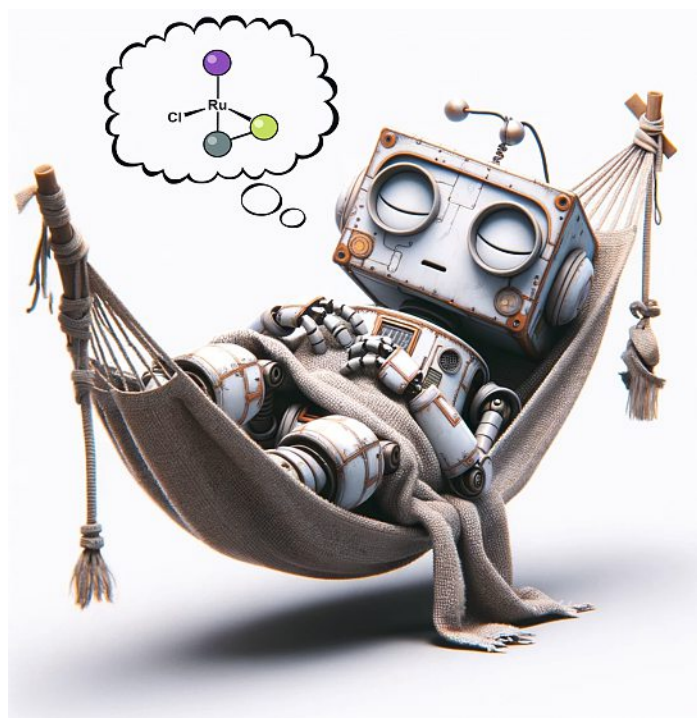
<https://doi.org/10.1002/anie.202317901>

University of Bern

With antimicrobial resistance (AMR) on the rise and a stagnant antibiotic pipeline, innovative drug discovery methods are essential. Metal complexes show promise as antimicrobial agents, but their exploration lags behind organic molecules. This study breaks new ground by applying machine learning (ML) to the discovery of metal-based medicines. Using 288 ruthenium arene Schiff-base complexes and ML models, antibacterial properties were assessed. Predictions for 54 new compounds were made, and their activity against methicillin-resistant *Staphylococcus aureus* (MRSA) surpassed the original library by 5.7 times, with a hit rate of 53.7% compared to 9.4%. This highlights ML's potential in improving success rates for novel metalloantibiotics and opens doors for broader applications in metal-based drug discovery.

Authors' comments:

“Machine Learning can be a very useful tool when applied properly and we think this work nicely highlights its yet to be explored potential in the field of metallodrugs.”



Catalyst Control Over Pentavalent Stereocentres

Anton Budeev, Jianyang Dong, Daniel Häussinger and Christof Sparr.*

Nat. Comm. **14**, **2023**, 8013

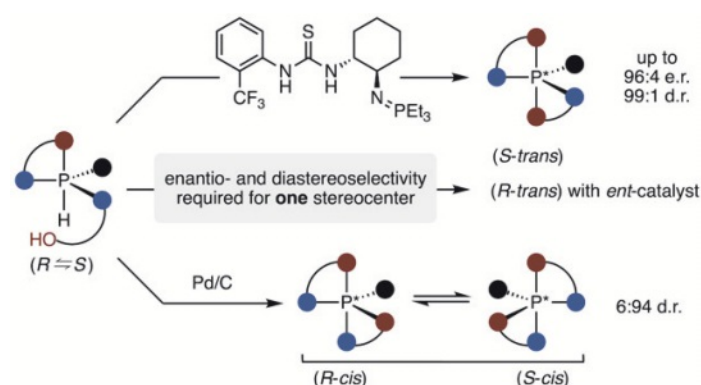
<https://doi.org/10.1038/s41467-023-43750-w>

University of Basel

Pentavalent phosphoranes are characterized by a fifth moiety attached to the central atom, which results in an extended stereochemical space beyond the classical Le Bel–van 't Hoff stereoisomerism ($>2^n$). Mastering control over high-valent stereocenters has proven to be a persisting challenge. In this work, a catalytic method allowing the selection of configurations in pentavalent stereocenters was developed. The catalytic feasibility of controlling pentavalent stereocenters was demonstrated using a bifunctional iminophosphorane thiourea catalyst. This catalyst enables precise control over enantio- and diastereomers emerging from a single stereocenter of pentavalent phosphoranes, yielding desired dioxophosphoranes with excellent yield and selectivity (up to 99% yield, 96:4 e.r. and 99:1 d.r.). Stereodivergent catalysis also allows selective access to each different diastereomeric state of the pentavalent phosphoranes, rendering the expanding stereochemical space of high-valent main group species selectively addressable.

Authors' comments:

“In view of the plethora of sophisticated catalytic methods addressing the two configurations of tetravalent stereocenters, we questioned if the larger stereochemical space ($>2^n$) of high-valent stereocenters is navigable. It was thus very gratifying to observe that catalyst control over pentavalent stereocenters is feasible.”



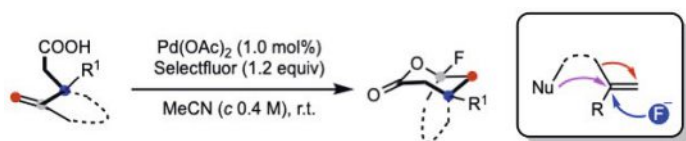
Palladium-Based Dyotropic Rearrangement Enables a Triple Functionalization of Gem-Disubstituted Alkenes: An Unusual Fluorolactonization Reaction

Qiang Feng, Chen-Xu Liu, Qian Wang, and Jieping Zhu*,
Angew. Chem. Int. Ed., **2024**, *63*, e202316393
<https://doi.org/10.1002/anie.202316393>
EPFL

This paper presents a novel Pd(II)-catalyzed migratory gem-fluorolactonization of gem-disubstituted ene-carboxylic acids for the synthesis of fluorolactones. The reaction is highly efficient and exhibits remarkable functional group tolerance, enabling the formation of both bridged and open-chain fluorolactones. The unique triple bond formation and selective ring-enlarging 1,2-alkyl/Pd(IV) dyotropic rearrangement are key features of this reaction. The high yield and versatility of this method makes it a valuable addition to the synthetic arsenal. The 1-fluoroalkyl carboxylates produced can be further transformed into ketoamides, bis(phenylthiol)hexanoic acids, and carboxylic acids.

Authors' comments:

"Integration of a 1,2-alkyl/Pd dyotropic rearrangement into a Pd(II)-catalyzed domino processes diverts completely the conventional reaction pathways to afford otherwise difficultly accessible products."



Solvent Dependent Folding of an Amphiphilic Polyaramid

Angélique Molliet, Samantha Doninelli, Linda Hong, Bettina Tran, Meron Debas, Stefan Salentinig*, Andreas F. M. Kilbinger*, and Tommaso Casalini*
J. Am. Chem. Soc. **2023**, *145*, 50, 27830.
<https://doi.org/10.1021/jacs.3c11026>
University of Fribourg

Polyaromatic amides with alternating *meta*- and *para*-linkages and hydrophilic and hydrophobic side chains were prepared *via* step growth polymerization. This allowed the induction of a helical conformation in water and the formation of a random coil in DMF. A comprehensive analysis utilizing ¹H-NMR spectroscopy, small-angle X-ray scattering, and multiangle (depolarized) dynamic light scattering provided information about the folded structure. Parallel tempering metadynamics simulations in the well-tempered ensemble (PTMetaD-WTE) revealed the complex free energy landscapes of a model polymer in DMF and water. With this multimodal approach, the structural analysis of these polymers in DMF and water was possible. It provided valuable insights and powerful predictive tools to guide the design and synthesis of future synthetic foldamers. It also demonstrates the need for thorough experimental and modeling studies to move the field forward.

Authors' comments:

"Our article was an interdisciplinary team effort. It combines polymer synthesis with thorough experimental and modeling analysis. Our new MetalJet SAXS at Chemistry in Fribourg will significantly add to these efforts."

