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Swiss Science Concentrates

A CHIMIA Column

Short Abstracts of Interesting Recent Publications of Swiss Origin

All-Heteroatom-Substituted Carbon Spiro Stereocenters: Synthesis, Resolution, Enantiomeric Stability, and Absolute Configuration

Olivier Viudes, Céline Besnard, Alexander F. Siegle, Oliver Trapp, Thomas Bürgi, Gennaro Pescitelli*, and Jérôme Lacour*

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https://doi.org/10.1021/jacs.5c06394
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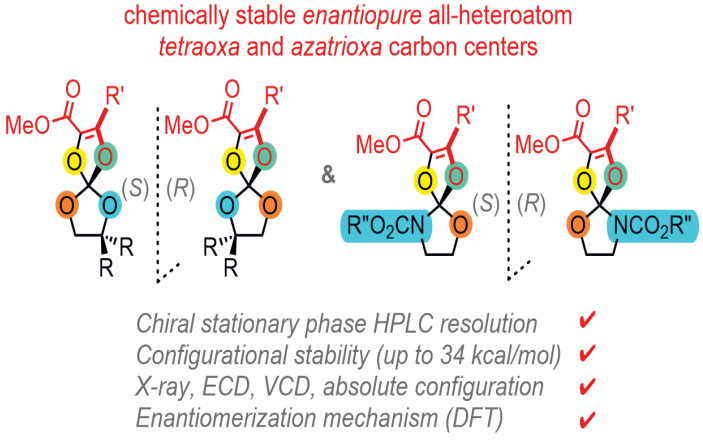
This study describes the CpRu-catalyzed synthesis of carbon stereocenters bearing exclusively oxygen and nitrogen substituents, prepared from cyclic carbonates or carbamates and α-diazo-β-ketoesters. Enantiomers were separated by chiral stationary phase HPLC. Tetraoxa derivatives exhibited cryptochirality ($g_{abs} \approx 10^{-5}$), whereas aza-trioxa analogues showed tenfold stronger chiroptical responses ($g_{abs} \approx 10^{-4}$), as determined by ECD and supported by TD-DFT. Crystalline spiro diastereomers confirmed structural and configurational assignments. Dynamic chromatography revealed high configurational stability, with enantiomerization barriers up to 27.6 kcal/mol for tetraoxa derivatives and 34.6 kcal/mol for aza-trioxa analogues (half-lives of 227 days and >84,000 years at 25°C). DFT analysis attributed these differences to preferential C–O versus C–N bond cleavage in the S_N1-like pathway. The work identifies spiro *ortho*-carbonates and *ortho*-carbamates as stable, enantiopure scaffolds for functional group manipulations.

Authors' comments:
"These stereogenic centers offer a novel manner of organizing 3D molecular space. They open up new degrees of freedom and imagination in chemical synthesis and catalysis."



Targeting the SHOC2–RAS Interaction in RAS-Mutant Cancers

Zachary J. Hauseman[a,c], Frédéric Stauffer[b,c], Kim S. Beyer[b,c], Sandra Mollé[b], Elena Cavicchioli[b], Jean-Remy Marchand[b], Michelle Fodor[a], Jessica Viscomi[a], Anxhela Dhembi[a], Stéphanie Katz[b], Beatrice Faggion[b], Mylene Lanter[b], Grainne Kerr[b], Daniela Schildknecht[b], Cornelia Handl[b], Danilo Maddalo[b], Carole Pissot Soldermann[b], Jacob Brady[a], Om Shrestha[a], Zachary Nguyen[a], Lukas Leder[b], Gregor Cremosnik[b], Sandra Lopez Romero[b], Ulrich Hassiepen[b], Travis Stams[a], Markus Linder[b], Giorgio G. Galli[b], Daniel A. Guthy[b], Daniel A. King[a], Sauveur-Michel Maira[b], Claudio R. Thoma[a], Veronika Ehmke[b,*], and Luca Tordella[b,*]

Nature **2025**, *642*, 232
https://doi.org/10.1038/s41586-025-08931-1
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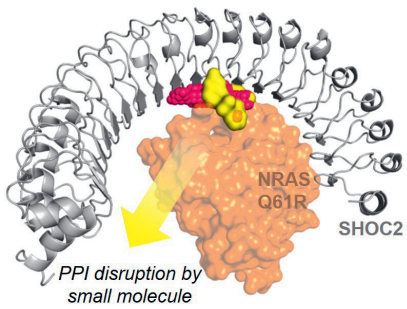
Mutations in RAS proteins are common drivers of human cancers. Although therapies targeting mutant KRAS have recently shown clinical promise, selective inhibitors for NRAS(Q61*), prevalent in melanoma, remain unavailable. This study highlights SHOC2, part of the holophosphatase SHOC2–MRAS–PP1C complex, as a key dependency in RAS(Q61*) mutant cancers. Biochemical, biophysical, and X-ray crystallographic studies reveal a binary interaction of SHOC2 and NRAS(Q61*). High-throughput screening and structure-based drug design led to small molecules and peptides binding to SHOC2, disrupting its interaction with mutant RAS. An optimized compound showed cellular activity and effective inhibition of MAPK signalling and cell proliferation in mutant melanoma models. These findings uncover a druggable interaction between SHOC2 and mutant RAS, offering a new therapeutic avenue at the core of the MAPK pathway.

Authors' comments:
"With this work we demonstrate that targeting the SHOC2-RAS interaction is an actionable therapeutic modality in RAS-mutant cancers. We show that this protein-protein interaction is pharmacologically actionable and provide a medchem strategy and a foundation for drug development to target RAS signalling."



Prepared by Cesare Berton, James Southwell, Titouan Chetot, Jonas Genz, Stanislav Prytuliak, Fan Liu, Eda Nisli, Deborah Bäcker, Samy Kichou, Dominik Roth, Laura Schüpke, Henrik Braband, and Jason P. Holland*
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Catalytic and Stoichiometric Stepwise Conversion of Side-on Bound Dinitrogen to Ammonia Mediated by a Uranium Complex

Mikhail S. Batov, Heather T. Partlow, Lucile Chatelain, John A. Seed, Rosario Scopelliti, Ivica Zivkovic, Ralph W. Adams, Stephen T. Liddle*, and Marinella Mazzanti*

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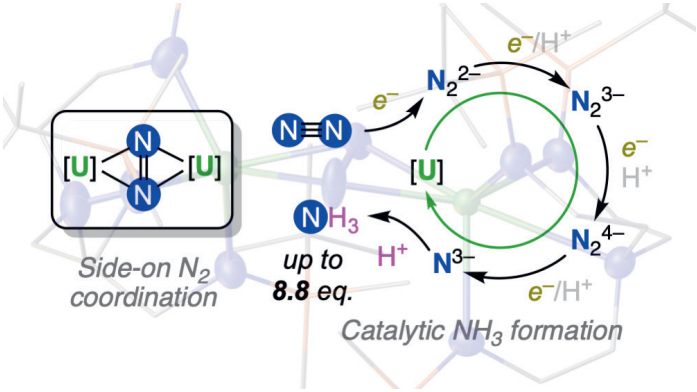
The authors of this study report the catalytic conversion of dinitrogen (N_2) to ammonia (NH_3) using a dinuclear uranium triamidoamine complex that uniquely features side-on N_2 binding – a mode relevant to both industrial and biological nitrogen fixation. Through combined experimental and quantum-chemical analysis, the researchers reveal a stepwise reduction of N_2 *via* four distinct side-on bound states (N_2, N_2^{2-}, N_2^{3-}, N_2^{4-}) leading to bridging nitrides, while uranium remains largely in the U(IV) oxidation state. Although catalytic turnover is currently limited, this work establishes the first example of molecular U-mediated N_2 to NH_3 catalysis involving side-on N_2 coordination. It broadens the known modes of N_2 activation beyond terminal and end-on binding, and emphasizes the role of polymetallic cooperativity. This breakthrough connects molecular systems to heterogeneous processes like Haber–Bosch and opens avenues for future catalytic transformations of dinitrogen into higher value molecular building blocks.

Authors' comments:
"We identified the first uranium-based molecular catalyst for the conversion of dinitrogen into ammonia. This system provides mechanistic insight of biological and industrial relevance into the catalytic conversion of dinitrogen into ammonia. We believe that in the future uranium chemistry can inform us in many more ways for advancing the use of dinitrogen as a sustainable feedstock."



Determination of the Experimental Minimal Formula of Metal-Organic Frameworks

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This work presents a rigorous approach to determining the true molecular composition of metal–organic frameworks (MOFs) by establishing their minimal, experimentally substantiated formulae. They develop a streamlined methodology centered on quantitative solution-state NMR spectroscopy, complemented by UV–Vis spectroscopy, to precisely quantify both organic and inorganic constituents within the frameworks. Emphasis is placed on the optimization of digestion protocols and NMR delay times to ensure analytical accuracy. By systematically enforcing charge balance and coordination constraints, the proposed analysis method reveals notable deviations from the idealized structural models commonly reported. Additionally, thermogravimetric analysis (TGA) is employed to assess the extent of water adsorption within MOF pores under experimental conditions. The general applicability of this methodology is demonstrated across a diverse selection of MOFs, including MOF-808(Zr), UiO-66(Zr/Ce), MOF-5(Zn), MIL-125(Ti), and MIL-100(Fe). This contribution offers a robust framework for accurate compositional characterization, facilitating enhanced understanding and design of MOF materials.

Authors' comments:
"We propose a simplified method for determining the minimal formula of MOFs by combining organic and inorganic characterization techniques. This allows for accurate compositional assignments beyond idealized structural models."