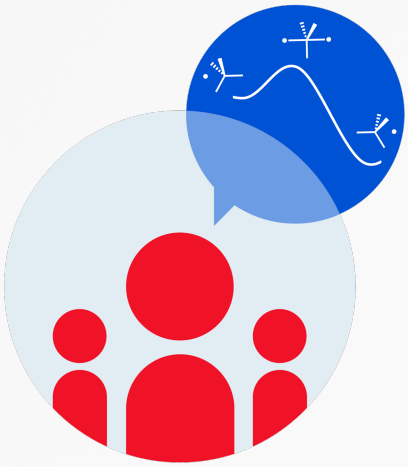
ESOR2023

Amsterdam

19-22 SEPTEMBER 2023



Book of Abstracts

19TH European Symposium on

Organic Reactivity

ESOR2023
Amsterdam

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Keynote Speakers

In Control with Light

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From the process of vision to the conversion of carbon dioxide in photosynthesis Nature has exploited the power of photochemical conversions in a remarkable way. Controlling reactivity with light offers tremendous opportunities as is highlighted among others by recent developments in photovoltaics, photo-redox catalysis in synthesis or light powered responsive materials.

In this lecture the use of light to control reactivity and motility in molecular, supramolecular and mesoscopic systems is illustrated. Exploring photochemical space, recent advances towards very fast photochemical click transformations, green photochemical based processes for materials and the use of light to induce responsive functions and progress in order to control rotary motion are discussed. The design, synthesis and functioning of molecular switches and rotary molecular motors will be presented with a prospect toward future dynamic molecular systems. In particular, recent approaches to control rotary speed through molecular design, tuning the excitation wavelengths and the efficiency of molecular motors are discussed.

Vision statement "Materials in Motion": Adv. Mater. 2020

Early Detection of Cancer by Metabolic Imaging

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The transition of a healthy cell to a cancer cell starts with the change of energy metabolism long before the cells proliferate uncontrollably and lead to anatomical changes (tumors, metastases) that can be visualized by conventional imaging. In particular, lactate/pyruvate metabolism is considered a hall-mark for cancer (Warburg effect). To detect cancer by metabolic imaging the sensitivity of magnetic resonance imaging (MRI) has to be increased by at least 5 orders of magnitude. This cannot be achieved by increasing the magnetic field strength. Hyperpolarization is currently the only method to achieve the necessary signal-to-noise ratio. The most commonly used method at present is DNP (dynamic nuclear polarization). For this, the sample (pyruvate) together with an organic radical is cooled to <1K in a strong magnetic field and irradiated with microwaves for about 2h to transfer the hyperpolarization of the electrons to that of ^{13}C. The hyperpolarization has a half-life (T_1 time) of ~2 min. The sample is then very quickly warmed to room temperature and injected into the patient. Several clinical studies have shown that this approach can be used to reliably detect prostate cancer and other types of cancer at a very early stage. However, the DNP method is so laborious and expensive that it is unlikely to find its way into clinical practice.

We take a different, much simpler approach to hyperpolarization. We use the spin order of para-hydrogen, transfer it as hyperpolarization to the 13C in 1-position of vinyl pyruvate, hydrolyze the ester and obtain hyperpolarized pyruvate. The process is much faster, simpler and less complex than DNP. We achieve hyperpolarization of up to 30%, which is sufficient for metabolic MRI.

[1] A. N. Pravdivtsev, F. Ellermann, A. Sirbu, A. Brahms, C. Assaf, R. Herges, and J.-B. Hövener, *Nature Commun*, accepted for publication

Accelerating Advances in Catalysis – Concepts, Insights, Strategies

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Modern catalytic strategies frequently rely on substantial optimization and high throughput screening for the identification of optimal conditions. To reach the next frontier in the construction of molecules via automation and programmable synthetic approaches, novel and fully orthogonal catalysis regimes are imperative to enable synthetic manipulations in an orthogonal manner to established bond forming approaches and associated catalysis regimes. This talk will give insights and developments towards this goal from our laboratory. The focus will be on multinuclear palladium[1] and nickel catalysis[2] of oxidation state (I), the exploration of organogermanes[3] as coupling partner as well as strategies to accelerate the identification of new catalysts[4] with data science.

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[2] A. Kapat, S. Sperger, S. Guven, F. Schoenebeck, *Science* **2019**, *363*, 391.

[3] A. Dahiya, A. G. Gevondian, F. Schoenebeck, *J. Am. Chem. Soc.* **2023**, 145, 7729.

[4] J. Hueffel, T. Sperger, I. Funes-Ardoiz, J. Ward, K. Rissanen, F. Schoenebeck, *Science* **2021**, *374*, 1134.

The Factors Determining Reactivity in Nucleophilic Substitution

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The S_N2 reaction has been studied in solution for more than a century and constitutes a cornerstone of structural and mechanistic chemistry. For the last five decades—in particular with the introduction of increasingly more advanced methods for mass spectrometric experimentation and quantum chemical calculation—it has become possible to obtain highly accurate descriptions of the energy landscapes[1] that determine the dynamics and kinetics of S_N2 reactions in the isolated gas phase and in cluster models, simulating also solution behaviour. In this talk we will discuss selected prototypical gas phase reactions, and report structure/reactivity relationships of S_N2 reactions linking reactivity, thermochemistry and chemical bonding.

[1] For recent reviews, see: E. Uggerud, in: I. Williams, N. Williams (Eds.) *Adv. Phys. Org. Chem.* **2017**, *51,* 1–57; T. A. Hamlin, M. Swart, and F. M. Bickelhaupt, *ChemPhysChem* **2018**, *19,* 1315 – 1330.

Mechanisms of Emergence in the Approach Toward De-Novo Life

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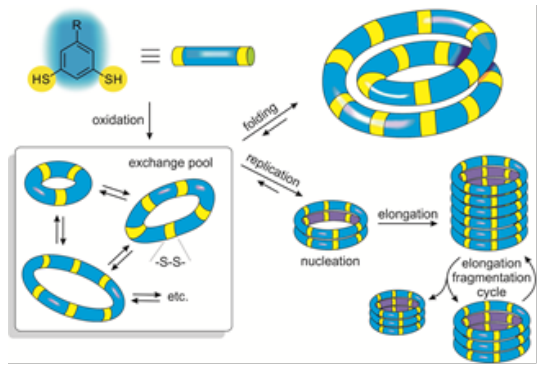
How the immense complexity of living organisms has arisen is one of the most intriguing questions in contemporary science. We have started to explore experimentally how organization and function can emerge from complex molecular networks in aqueous solution. We focus on networks of molecules that can interconvert, to give mixtures that can change their composition in response to external or internal stimuli. Molecular recognition within or between molecules in such mixtures leads to their mutual stabilization, which drives the synthesis of more of the privileged structures (see Figure). As the assembly process drives the synthesis of the very molecules that assemble, the resulting materials can be considered to be self-synthesizing. Intriguingly, in this process the assembling molecules are replicating themselves, where replication is driven by self-recognition of these molecules in the dynamic network.[1] When such systems are operated under far-from-equilibrium flow conditions, adaptation of the replicators to a changing environment can occur.[2]



Replicators that are able to catalyse reactions other than their own formation have also been obtained, representing a first step towards metabolism.[3] Rudimentary Darwinian evolution of these systems has been achieved[2] and the prospect of synthesizing life de-novo is becoming increasingly realistic.[4]

[1] J.M.A. Carnall, C.A. Waudby, A.M. Belenguer, M.C.A. Stuart, J.J.-P. Peyralans, S. Otto, *Science* **2010**, *327*, 1502.
[2] K. Liu, A. Blokhuis, C. van Ewijk, A. Kiani, J. Wu, .W.H. Roos, S. Otto *Nat. Chem.* **2023**, *in press.*
[3] (a) G. Monreal Santiago, K. Liu, W.R. Browne, S. Otto, N*at. Chem.* **2020**, *12*, 603. (b) J. Ottelé, A.S. Hussain, C. Mayer, S. Otto, *Nat. Catal.* **2020**, *3*, 547.
[4] P. Adamski, M. Eleveld, A. Sood, A. Kun, A. Szilágyi, T. Czárán, E. Szathmáry, S. Otto, *Nat. Rev. Chem.* **2020**, *4*, 386.

Concerted and Stepwise Cycloadditions: Applications to Medicinal Chemistry and Particle Physics

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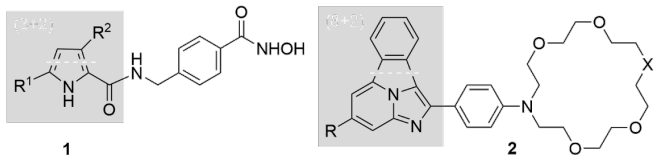
Different cycloadditions that yield cyclic compounds of biological or photophysical interest will be presented in this lecture. In all these examples, a combined computational and experimental approach has been used.

The concerted or stepwise formal (3+2) cycloaddition between azomethine ylides (formed in situ from the corresponding imines) and π–deficient alkenes will also be discussed. In our group, we have developed different catalysts to promote this reaction.[1] The (3+2) cycloadducts thus prepared are unnatural prolines that can generate anticancer compounds of type **1**.[2] This reaction has been extended to biopolymers such as DNA and CTPR proteins to generate artificial Huisgenases.[3]

We have also explored higher order (8+2) cycloadditions to generate fluorescent indicators of type **2** that capture Ba^{2+} cations produced in the Xe-136→Ba-136^{2+}+2e$^-$ neutrinoless double beta decay nuclear reaction. This process could eventually demonstrate that the neutrino is its own antiparticle, thus explaining the matter-antimatter asymmetry in the Universe.[4,5]



1 **2**

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[2] E. Conde, I. Rivilla, A. Larumbe, F. P. Cossío, *J. Org. Chem.* **2015**, *80*, 11755.

[3] I. Rivilla, M. Odriozola-Gimeno, A. Aires, A. Gimeno, J. Jiménez-Barbero, M. Torrent-Sucarrat, A. L. Cortajarena, F. P. Cossío, F. P. *J. Am. Chem. Soc.* **2020**, *142*, 762.

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Photochemistry & Organocatalysis: New Radical Opportunities

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The chemical reactivity of electronically excited molecules differs fundamentally from that in the ground state. This is the underlying reactivity concept of photochemistry,[1] which has traditionally allowed the development of unique chemical transformations not achievable via conventional ground-state pathways. For example, an excited-state molecule is both a better electron-donor (i.e. a better reductant) and electron-acceptor (i.e. a better oxidant) than in the ground state. This explains why the light excitation of organic molecules can unlock unconventional reactivity manifolds.

In this context, our laboratory has been exploring the potential of some organocatalytic intermediates to directly reach an electronically excited state upon visible-light absorption to then switch on novel catalytic functions that are unavailable to ground-state organocatalysis.[2] Studying the mechanism[3] of these photochemical approaches allowed us to expand the synthetic possibilities offered by the excited-state reactivity of organocatalytic intermediates and to develop enantioselective radical processes.[4]

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Mechanistic Evaluation of Bis-aminocyclopropenylidenes as Nucleophilic Organocatalysts

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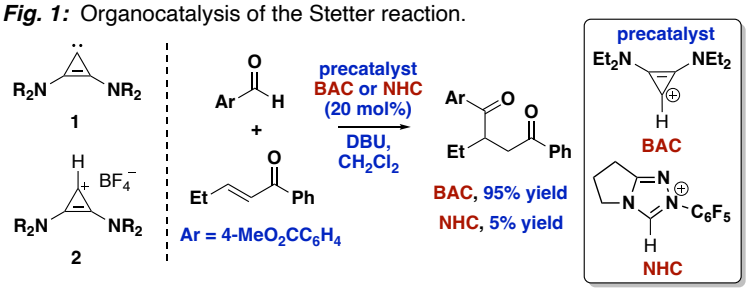
Bis(amino)cyclopropenylidenes **1** (BACs) have recently shown promise as nucleophilic organocatalysts for acyl anion and extended umpolung reactions owing to their orthogonal chemoselectivities to the well-studied N-heterocyclic carbenes (NHCs).[1] Alkyl amino BACs efficiently promote the challenging intermolecular Stetter reaction (Fig. 1) with minimal contribution from a competing benzoin reaction even with more 'difficult' Stetter acceptors such as β-alkyl substituted-(α,β-unsaturated)-ketones. We report our synthetic, structural and kinetic evaluation of BAC-catalysed benzoin and Stetter reactions including the isolation of the common first intermediate on the reaction pathway of both transformations. Comparison with our earlier studies of the analogous NHC-catalysed processes[2] enables mechanistic insight into the two classes of nucleophilic organocatalyst. We additionally report our kinetic evaluation of the proton transfer reactions of the bis(amino)cyclopropenium conjugate acids **2**, commonly used as pre-catalysts for **1**, which may be compared with the protofugalites of a broad range of conjugate acid pre-catalysts of NHCs.

Fig. 1: Organocatalysis of the Stetter reaction.



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[2] (a) J. Zhu, I. Moreno, P. Quinn, D. S. Yufit, Lijuan Song, C. M. Young, Z. Duan, M. Hall, M. R. Probert, A. R. Tyler, P. Waddell, A. D. Smith and A. C. O'Donoghue, *J. Org. Chem.*, **2022**, *87*, 4241; (b) R. S. Massey, J. Murray, C. J. Collett, J. Zhu, A. D. Smith and A. C. O'Donoghue, *Org. Biomol. Chem.*, **2021**, *19*, 387; (c) Z. Duan, C. M. Young, J. Zhu, A. M. Z. Slawin, A. C. O'Donoghue and A. D. Smith, *Chem. Sci.*, **2023**, *14,* 162.

Invited Speakers

Exploring Chemical Glycosylation Reactions: Can We Control Them?

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The synthesis of complex carbohydrates is of paramount importance for medical and biological research. The principal challenge in the chemical synthesis of carbohydrates is the stereoselective installation of glycosidic bonds. Glycosidic bonds, uniting two building blocks to form more complex carbohydrates, can either exist as 1,2-*cis* or 1,2-*trans* diastereomers, and the nature of the linkage has a profound influence on the structure and function of the carbohydrates. Insufficient knowledge of the operative mechanism of the glycosylation reaction at the molecular level thwarts its rational development. Therefore, we used state-of-the-art computational and experimental techniques to obtain critical insight into the reaction mechanism. We found that glycosyl cations can act as key reactive intermediates and mapped clear structure-reactivity-stereoselectivity relationships for these species. The insights gained in these studies paved the way to synthesize a set of highly complex mycobacterial glycolipids (Figure 1), delivering more and more complex glycans to fuel glycobiological and glycomedical research.[1]

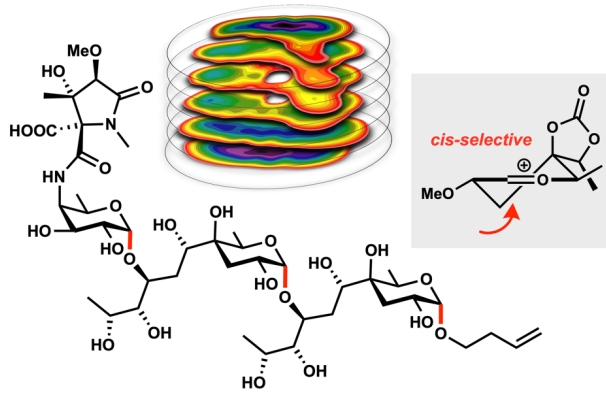

Figure 1. Mapping the behavior of glycosyl cations by computational and experimental techniques to understand these reactive intermediates in the assembly of complex carbohydrates.

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Catalyst Control in Complex Natural Product Synthesis

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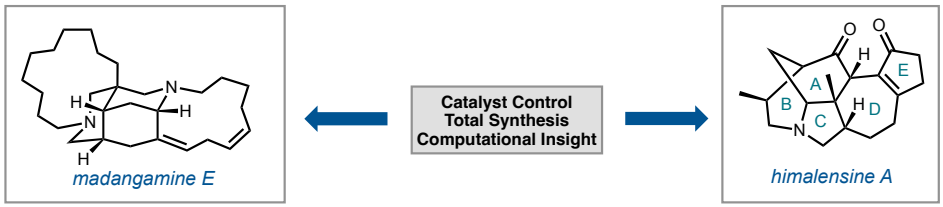
The identification, optimisation and use of new chiral catalysts and catalytic systems to bring about new reactivity and impart high levels of stereocontrol in the key enantiodetermining bond forming step of some complex natural product syntheses will be presented. The scope of the arising methodologies, the route to the target molecules and the origin of the stereoselectivity as revealed by computational calculations using DFT will also be presented.[1,2]



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The Pauli Repulsion Lowering Concept in Catalysis

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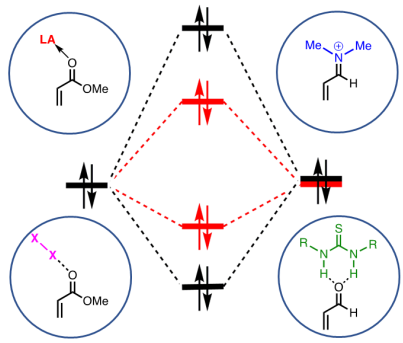
In this talk, we will summarize our recently proposed "*Pauli-repulsion lowering*" concept as a novel physical mechanism governing the catalysis in fundamental processes in organic chemistry such as the Diels-Alder cycloaddition reaction or the Michael addition reaction.[1,2]

With the help of the Activation Strain Model of reactivity combined with the Energy Decomposition Analysis method,[3] we found that the traditional *LUMO-lowering* catalysis concept, based on qualitative frontier molecular orbital (FMO) theory, is rather incomplete and cannot be used to rationalize the mode of activation of catalysts in these transformations. Instead, the catalyst induces a significant polarization in one of the reactants which reduces the two-orbital, four-electron Pauli-repulsion between the involved reagents. This becomes the ultimate physical factor responsible for the acceleration of the catalyzed reaction as compared to the uncatalyzed reaction.



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Folding single polymer chains into functional materials

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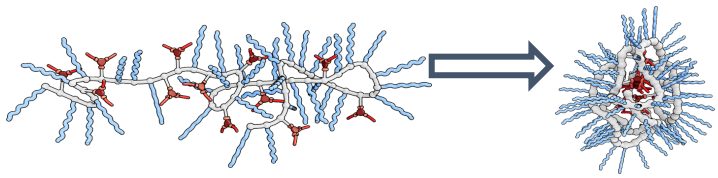
Inspired by proteins, we investigate the single-chain folding of synthetic polymers into defined 3D structures using a combination of solvophobic and hydrogen-bonding interactions.[1] Benzene-1,3,5-tricarboxamides (BTAs) are applied as the structuring motif to induce single chain folding.[2] In water, we observe that the balance between hydrophobic, structuring and hydrophilic moieties is crucial to obtain compact, stably folded polymer conformations of nanometre-size.[3] Preferred global conformations of the nanoparticles can be stabilized by using additional chemical crosslinks via light-induced reactions, affording stable and fluorescent nanoparticles.[4,5] The hydrophobic interior of the nanoparticles also allows to entrap catalysts, covalently or physically.[6,7] Together with the concentrator effect, where hydrophobic substrates accumulate in hydrophobic compartments in water,[8] substrates are rapidly converted to products, even in complex, cellular media.



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En route to more energy efficient silicon hydrides using molecular catalysis

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Hydrosilanes are useful compounds for the production of a variety of organosilicon compounds through hydrosilylation of alkenes or dehydrocoupling reactions.[1,2] They also promote, in mild conditions, the reduction of functional groups such as esters[3,4] or amides[5] with high selectivity. In comparison with apolar dihydrogen, the couple $E^0(Si(OEt)_{4(l)}/SiH_{4(g}$ (–0.51 V vs. NHE) and the polarized and weaker Si–H bond (BDE_{Si-H} = 95 kcal.mol^{-1} < BDE_{H-H} = 104 kcal.mol^{-1}) offer some thermodynamic and kinetic advantages[6] relevant for the reduction of oxygenated chemical feedstocks that could replace oil in the long run (lignin, plastics and CO_2).[7–9] Because classical routes for the production of hydrosilanes are energy demanding,[10,11] alternative catalytic syntheses that would transform Si–X (X = halides, alkoxides) precursors into Si–H are appealing. This endeavor has motivated us to explore the synthesis, use, and recycling of energy efficient surrogates of hydrosilanes, namely silylformates, in hydrosilylation chemistry.[10-12] In addition, our recent findings in hydrogenolysis routes to hydrosilanes will be presented using transition metal based catalysts as well as metal-free catalysts.[13-15]

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Geometrically Constrained Lewis Acids and Bases for Frustrated Lewis Pair Chemistry

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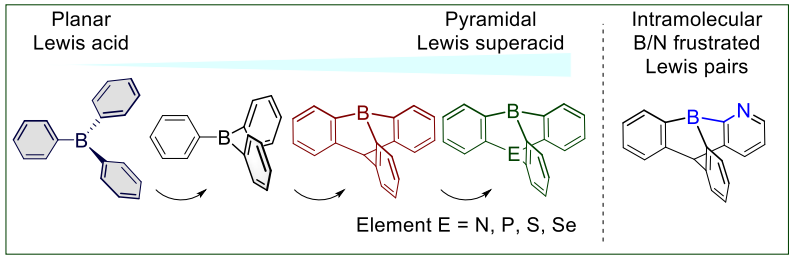
Frustrated Lewis pairs and element / ligand bifunctional compounds mimicking the reactivities of transition-metal complexes are increasingly used as catalysts for small molecules activations and inert bonds functionalization.[1] Our group has recently devoted significant efforts towards the development of new classes of boron Lewis superacids with unique pyramidal geometries featuring unprecedented reactivities toward small molecules.[2] Experimental and computational mechanistic investigations of FLPs mediated hydrogenations, C-H borylations and alkynes functionalizations proved to be a powerful strategy to design new frustrated Lewis pairs with unusual structures and reactivities.[3]



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Indigoid molecular switches and machines

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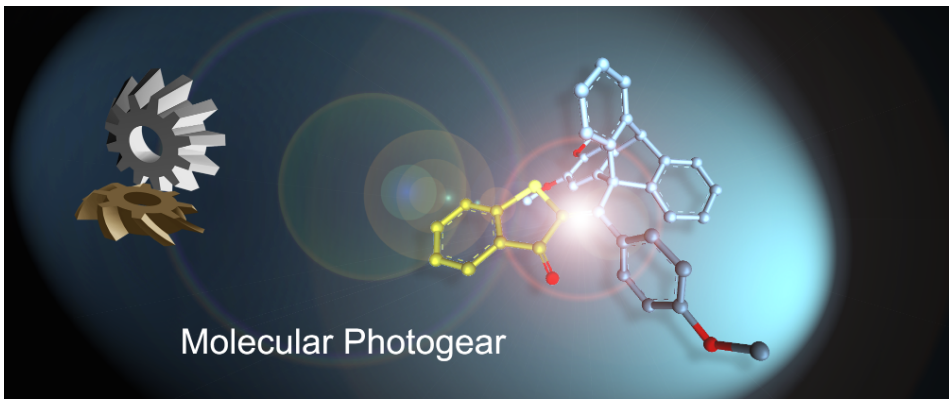
The concept of miniaturization promises almost unlimited possibilities for the development of advanced and futuristic technology. Be it smart materials, nano- medicine or even artificial life – for all these areas synthetic chemistry is the ultimate foundation. In this lecture research on molecular switches and machines will be the central topic to answer one fundamental question: how can one miniaturize deliberate motions and mechanical processes and how can such they be controlled and applied? To this end conceptual ideas spanning synthetic organic, physical, photo, and supramolecular chemistry will be explored while rediscovering the colorful chemistry of the late 19th and early 20th century.[1,2]



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Influence of Mechanical Force and External Pressure on Chemical Reactivity

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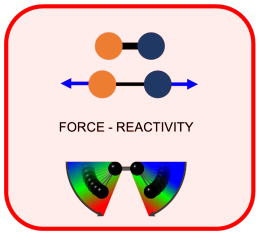
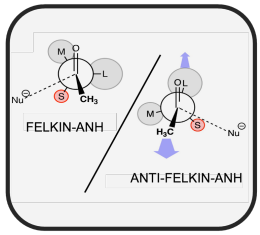
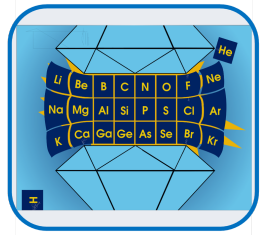
Mechanical activation of single molecules and the application of external pressure to activate chemical processes have attracted much attention recently. Important questions emerging are “where” to apply a mechanical force and “what” happens to chemical reactivity upon application of mechanical forces and pressure.

We aim at answering these questions for simple systems within the framework of conceptual density functional theory.[1] By stretching diatomic molecules, the responses of reactivity indices were investigated.[2] The effect of straining bond angles was probed for linear and cyclic alkynes, bridging the concept of ring strain and mechanochemistry. Upon bending, the reactivity of the triple bond increases which is reflected in faster click reactions between cyclic alkynes and azides, as compared to the linear alkynes.[3] Next, we explored the mechanical activation of more challenging systems by quantifying the changes in the potential energy surfaces induced by mechanical stress. As an example, we discuss the circumvention of the Felkin-Anh diastereoselectivity upon stretching the ketone with a mechanical pulling force.[4] In a final part, we investigate the effect of pressure on atomic chemical concepts, such as the electronegativity, hardness and electrophilicity.[5]







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Reactions in crystals and limits of the concept of reaction mechanism

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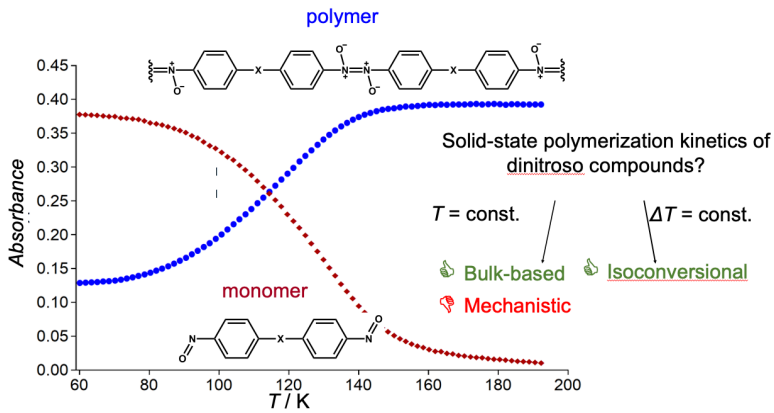
Dimerization of aromatic nitroso compounds in crystalline and polycrystalline phase represents the model for studying the nature of the thermally induced chemical reactions in solids. Since the rates of these thermally induced reactions are measurable in the real time, the model opens the opportunity for the evaluation of activation parameters of solid-state reactions. However, the processes in crystals comprise not only chemical reactions but also diverse types of phase transformations. Accordingly, the classical concept of the reaction mechanism, which is normally applied for the studies of reactions in solution and in the gas phase, is of very limited use in the reactions in crystals or polycrystalline phases. In this presentation we demonstrate how basically different kinetic mechanistic models for fitting the kinetic curves of the solid-state polymerizations of di- and polynitroso compounds provide almost the same activation parameters[1] In addition, some of the polymers investigated in this study are candidates for the new type of organic semiconductors. [2]



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New Polar and Radical Methods for the Formation of Carbon-Phosphorus Bonds: A Mechanistically-Driven Approach

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Organophosphorus compounds are important scaffolds that have gained tremendous attention owing to their prevalence in various areas ranging from agriculture to medicine. Although there are many effective synthetic methods for forming carbon-phosphorus bonds, some of them are prone to the use of harsh reaction conditions.

The lecture will cover recent developments from our group that aim to provide practically simple methods for synthesising organophosphorus scaffolds from readily available phosphorus sources. It will also underline the importance of physical organic tools in understanding the reaction mechanisms and the design of new transformations.[1]

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A Journey to the Land of Polycyclic Aromatic Systems

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Polycyclic aromatic systems (PASs) are among the most prevalent and impactful classes of compounds in the natural and man-made world. Though aromatic systems have captured the fascination of chemists for almost two centuries, a general conceptual framework for understanding and predicting the structure-property relationships of polycyclic systems remains elusive. Yet, the structure-property relationships of PBHs have both conceptual and practical implications and understanding them can enable design of new functional compounds. We address this gap using a combination of computational chemistry and data science tools.

We first interrogated polybenzenoid hydrocarbons using a combination of traditional computational techniques, including characterization of their aromatic character in the S_0 and T_1 states (described with the NICS metric), their spin density in the T_1 state, and their S_0—T_1 energy gaps. Regularities were revealed that allowed for simple and intuitive design guidelines to be defined.[1]

To verify these guidelines in a data-driven manner, we generated a new database – the COMPAS Project[2] and developed two types of molecular representation to enable machine- and deep-learning models to train on the new data: a) a text-based representation[3] and b) a graph-based representation.[4]

In addition to their predictive ability, we demonstrate the interpretability of the models that is achieved when using these representations. The extracted insight in some cases confirms well-known “rules of thumb” and in other cases disproves common wisdom and sheds new light on this classical family of compounds.

Finally, we implemented a generative model that design novel PASs with targeted properties in an effective and efficient manner, demonstrating the first inverse design of PASs.[5]

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π-Conjugated Oligoradicaloids and Anions: Aromaticity, Magnetism, and Non-covalent Interactions

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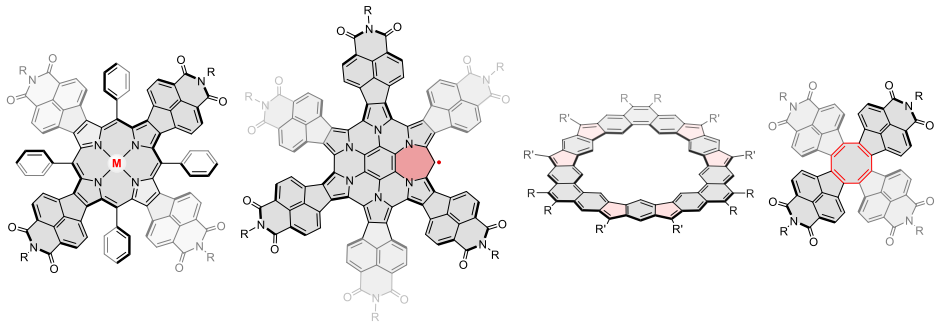
Charge and spin distribution in π-conjugated molecules depends in a complex fashion on the size topology of the ring system, placement of heteroatoms and molecular curvature. In large non-benzenoid systems, structure–property correlations become particularly intricate, showing effects of local and global aromaticity, mixed valence character, and non-equivalence of spin-interaction pathways. This talk will highlight a variety of π-conjugated open-shell molecules recently developed by our group, characterized by linear,[1,2] branched,[3] macrocyclic,[4,5] or 2D-fused structures.[6] We will show how these systems respond to changes in spin state and charge and how some of them can be used for coordination of cations and anions.



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Surface-mediated organic reactivity: chemistry on and with the surface

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Molecular chemistry usually does not care about surfaces. Surface science often deals with small inorganic molecules (e.g., CO, N_2) targeting catalysis or focuses on chemically unreactive larger adsorbates (e.g., porphyrins). We explored the surface chemistry of organic molecules on semiconductor surfaces in the last decade and discovered many surprising and unexpected reactivity.

Using computational approaches ranging from density functional theory (DFT) over molecular dynamics (AIMD) approaches up to modern bonding analysis approaches using energy decomposition analysis for extended systems (pEDA),[1] we could unveil and quantitatively support the previously proposed concept of the surface as molecular reagent.[2] Nuclear substitution, cycloadditions and dispersion-dominated reactivity have been discovered for organic reactants on silicon surfaces.[3] But the surface can also serve as more or less innocent platform for organic reactivity. We explored this with the target of bottom-up construction of hybrid organic-inorganic interfaces in intense collaboration with experimental UHV-based surface science approaches.[4]

In all investigations, we start from understanding experimental data and thrive to achieve predictive computational results based on quantitative analysis leading to helpful concepts for the challenging and often unintuitive organic chemistry on and with the surface.

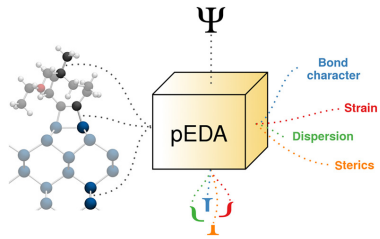

Figure. Quantitative bonding analysis helps disentangle organic reactivity on surfaces.

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Controlling Chemical Reactivity in Time and Space

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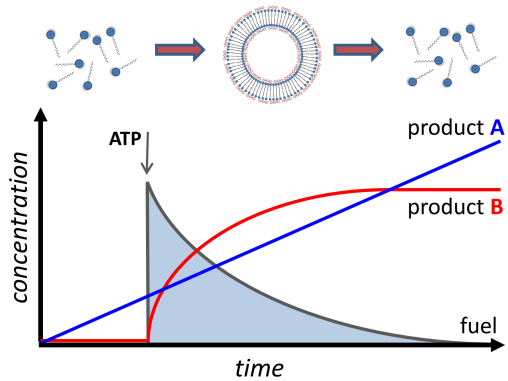
Nature has an extraordinary capacity to process information through the activation of sophisticated signal transduction pathways. Likewise, the transition of chemistry into an information science able to translate information from the environment into functional output requires chemical systems with a differentiated response to different environmental cues. Here, we show how chemical fuels can be used for the transient upregulation of chemical reactions in a complex chemical system and show that different fuels can evoke different responses from the same system. Furthermore, we show that spatial control can be achieved by delivering chemical fuels locally to an hydrogel matrix.



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Contributed Talks

A Mechanistic Approach to Nonenzymatic Reduction Reactions: When Metals Take the Role of Enzymes

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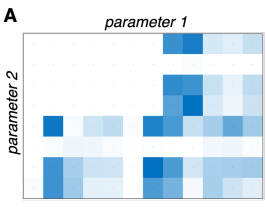
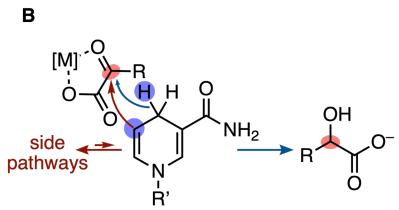
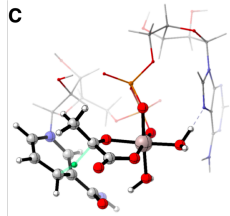
Recent work has shown that simple metals or metal ions can promote multiple reactions of biochemical metabolism that are typically catalyzed by enzymes.[1] Reduction reactions are essential within biochemical metabolism, but it remains unclear how they emerged before the availability of enzymes at the origins of life.[2] To address this question, we have performed a physical-organic investigation on the reduction reactions of carbonyl groups by the biochemical cofactor NADH (see Figure). By combining high-throughput screening and statistical reaction optimization, we have identified conditions under which catalytic amounts of metal ions drastically enhance the reactivity of keto acids enabling their nonenzymatic reduction by NADH. Kinetic studies, isotope-labeling experiments, and tracing of side pathways allowed us to establish the mechanism of the reaction. Notably, the chirality of the hydride donor NADH is partially translated to the products. Extensive DFT computations allowed us to identify intramolecular hydride transfer within a highly organized supramolecular structure to be responsible for the observed chirality transfer. The identified reaction conditions constitute the missing link in enabling nonenzymatic reductions in early metabolism and are the first example of a reaction where a metal ion mimicking enzyme function enables chirality transfer of a biochemical reaction.



Initial steps: high-throughput screening and response-surface optimization



Analysis of the mechanism with in-situ analytics, kinetics, labeling studies, analysis of side pathways



Computational analysis of mechanistic key steps for chirality transfer

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Ab initio and machine learning chemistry of radical ions

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Organic radical ions are ubiquitous across chemistry and biology, functioning as intermediates in organic synthesis, charge shuffles in electronic devices, and active forms in biochemical transformations. Yet, while various approaches exist to quantify and compare stabilities of neutral radicals, no general scale exists for radical ions. Here, we will present a scheme for assessing relative stabilities of charged open-shell systems based on simple thermodynamic quantities and demonstrate its utility for various types of radical ions. Another limitation in predicting the properties of radical ions arises when employing popular machine learning techniques: most molecular representations are unable to distinguish between molecules with identical or similar geometries but different charges and spins. To address this challenge, we have developed a quantum-inspired molecular and atomic representation called matrix of orthogonalized atomic orbital coefficients (MAOC).[1] MAOC is based on a cost-effective localization scheme that represents localized orbitals *via* a predefined set of atomic orbitals. MAOC can uniquely describe compounds with identical compositions and geometries but distinct charges and spin multiplicities. We demonstrate the performance of MAOC in conjunction with kernel ridge regression for two new datasets containing radical ions – N-HPC-1 consisting of N-heteropolycycles and REDOX consisting of redox-active molecules (e.g., nitroxides, quinones, cyanides, etc.).

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Scope and Limitations of Iodine Catalysis

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Molecular iodine is known for over a century to be an effective and mild catalyst, yet the underlying activation mode remained unknown.[1,2] Recently, experimental and computational investigations showed that a halogen-bond activation is the most likely pathway in Michael additions, Nazarov cyclizations, and Diels-Alder reactions.[3] In contrast, an iodonium pathway was considered to operate in the iodine-catalyzed carbonyl-olefin metathesis.[4]

As iodine-catalyzed reactions typically occur under mild conditions, we wanted to probe the applicability and limitations of iodine catalysis in other synthetically important transformations. We will discuss the influence of molecular iodine on Claisen rearrangements[5] and carbonyl-alkyne metatheses. Our experimental and computational investigations provide new and simple synthetic protocols as well as detailed mechanistic insights of these reactions.

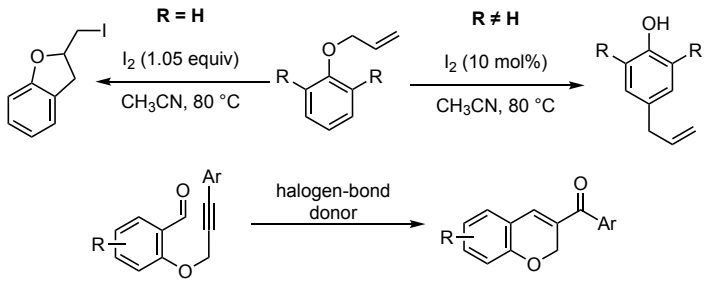

Figure 1: Application of iodine catalysis in the [3,3]-sigmatropic rearrangements (top) and of halogen-bond donors in the carbonyl-alkyne metathesis (bottom).

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Efficient measurements of nucleophilicities

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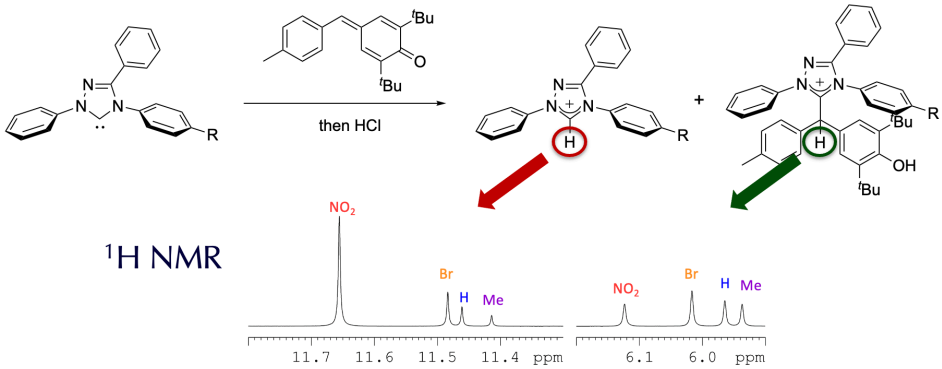
N-Heterocyclic Carbenes (NHCs) are widely used as nucleophilic organocatalysts, though structure activity relationships for these compounds are limited:[1] there are only direct nucleophilicity measurements for seven NHCs.[2,3] Our group has looked at alternative ways to indirectly assess nucleophilicity, including pK_a values[4] and electron donation measures,[5] as direct measurement of nucleophilicity a non-trivial equipment set-up.

We present a new methodology to determine the relative nucleophilicity of NHCs *via* competition reactions.[6] Based on the simple requirements that no reaction go to completion and that the extent of reaction is measurable, the reaction of multiple competing nucleophiles with a single electrophile generates relative rates (and hence relative nucleophilicities) in a single reaction vessel. This methodology does not need specialist set-up and is able to measure nucleophilicity parameters rapidly and with uncertainties generally less than ± 0.3. This development allows for the close comparison of structurally similar NHCs as well as the rapid determination of nucleophilicity for highly varied nucleophiles.



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In the CORE of Olefination: an *Umpolung / Eigenbase* Update

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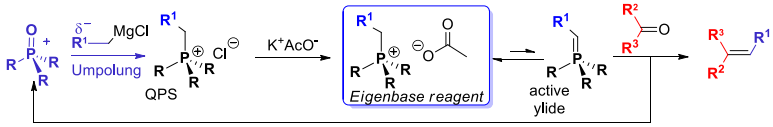
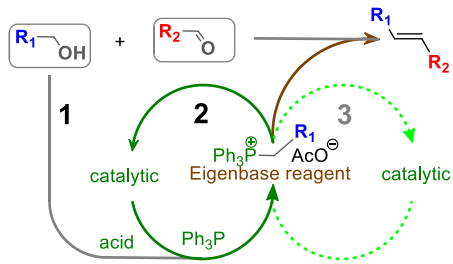
The Wittig olefination reaction has just got a very significant makeover. First, the annoying phosphine oxide by-product can now be used as the starting material. It can be converted directly to quaternary phosphonium salt, QPS, via new fast and high-yielding "*Umpolung* quaternization".[1] We have eliminated the waste problem and olefinations can be run using phosphine oxide and avoiding phosphines at the interim stages.



Second, we have developed novel ion-pair carboxylate reagents containing its own (hence *Eigenbase*) endogenous anionic base. The *Eigenbase* reagents work in the absence of added bases[2] and this process is hinged on the interplay of structure and function of phosphonium carboxylate ion pairs in different solvents.[3] The olefinations furnish a range of alkenes in high yields, no protecting groups are needed.



Third, most *Eigenbase* reagents can be prepared directly from alcohols as shown in route 1. This variant termed acidic **s**toichiometric **o**lefination **re**action (SORE) avoids use of halogen derivatives, bases and metal salts altogether.[4]

Fourth, we went a step further and have achieved shortcut catalytic cycle 2 and develop cycle 3. These circular olefination reactions (CORE) are single-step catalytic protocols. The venerable Wittig-type olefination is done without phosphorus waste, protecting groups, organic halides, metal salts and bases. Ironically, it is now acid-catalysed.

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Activation of E–H bonds (E=O, S, N) at Bicyclic Silanides

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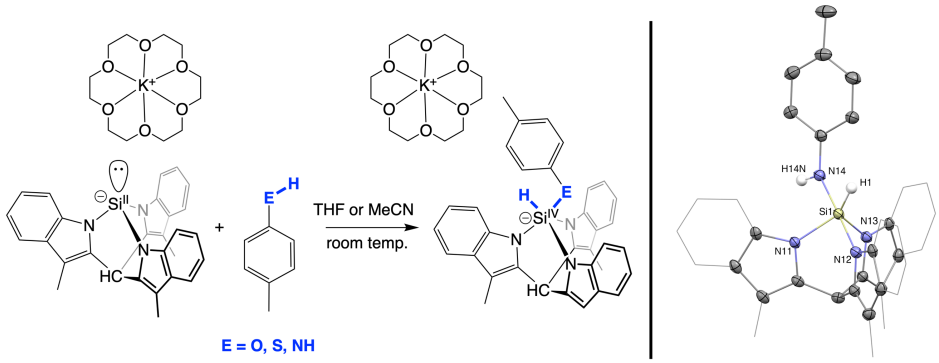
To minimize the environmental impact of synthetic chemistry, new catalytic methods based on non-traditional elements are desirable. High abundancy, low cost, and low toxicity would make silicon particularly attractive for sustainable catalysis. Promisingly, reduced Si^{II} compounds such as silylenes (R_2Si:) have been found to activate challenging chemical bonds, but catalytic cycles relying on the Si(II/IV) redox couple are exceedingly rare.[1]

In contrast to their neutral congeners, the reactivity of silanides (R_3Si^-) is mostly nucleophilic, and they are useful synthetic intermediates towards silane derivatives. In this contribution, we show that incorporation of at the negatively charged Si atom at the bridgehead position of a bicyclic structure[2,3] opens new reactive pathways. Namely, E–H (E=O, S, N) can undergo a formal oxidative addition reaction to form pentacoordinate hydrosilicates. The mechanism of these reactions is investigated by a combination of experimental and theoretical methods, and consequences for the future design of Si-based catalysts are discussed.



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Revising the Rationale Behind C–H Bond Distances

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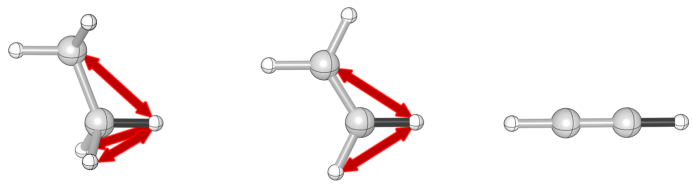
A fundamental and ubiquitous phenomenon in chemistry is the contraction of the C–H bond going from, for example, ethane to ethylene to acetylene. As introduced by Linus Pauling more than 90 years ago,[1] and described in most chemistry textbooks,[2] this structural trend originates from the increasing percentage of *s*-orbital character of the hybrid orbital, as the carbon atom involved changes in s–p hybridization from sp^3 to sp^2 to sp. This results in an optimal bond overlap at shorter C–H bond distances. During this talk, it will become evident that this rationale behind this structural phenomenon is incorrect. By quantum-chemical bonding analyses based on Kohn-Sham molecular-orbital theory,[3] I will show that this C–H bond contraction is, in fact, caused by a diminishing steric (Pauli) repulsion between the substituents around the pertinent carbon atom as the coordination number of the carbon atom of interest decreases from 4 to 3 to 2 along ethane, ethylene, and acetylene.[4]



ethane ***long*** **ethylene** ***medium*** **acetylene** ***short***

Figure 1. The contraction of the C–H bond going from ethane to ethylene to acetylene as a consequence of the diminished steric (Pauli) repulsion between the substituents around the pertinent carbon atom.

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A Tour to the Upper Limit of Nucleophilicity Scales: Mesoionic *N*-Heterocyclic Olefins

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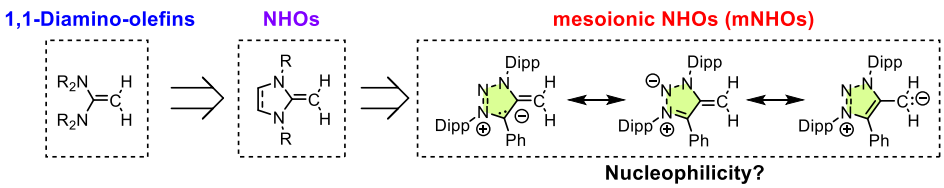
Electron-donating or -withdrawing substituents strongly influence the reactivity of olefinic π-systems. The electron-donating effect of the two amino groups in 1,1-diamino-olefins can be enhanced by embedding them in conformationally rigid *N*-heterocyclic olefins (NHOs).[1,2] In 2020, Hansmann et al. showed qualitatively that the donor properties of exocyclic $=CH_2$ groups in classical NHOs further increase in mesoionic NHOs (mNHOs).[3] To determine the nucleophilicity of mNHOs, we investigated the kinetics of mNHO reactions with reference electrophiles of known electrophilicity *E* and evaluated the experimental rate constants k_2 by the Mayr-Patz equation (MPE).[4,5]

$$\lg k_2(20°C) = s_N(N + E) \qquad \text{(MPE)}$$

This classification shows that mNHOs represent the currently most reactive nucleophiles on the nucleophilicity (*N*) scale.[6] The nucleophilicity of mNHOs correlates well with DFT-calculated methyl cation affinities which facilitates the design of novel mNHO structures with predictable, tailor-made reactivity and affinity towards electrophiles. We will show that *N* (and s_N) of mNHOs are a reliable basis for studies of the synthetic potential of mNHOs.



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Through-space stabilization of an imidazolium cation by aromatic rings

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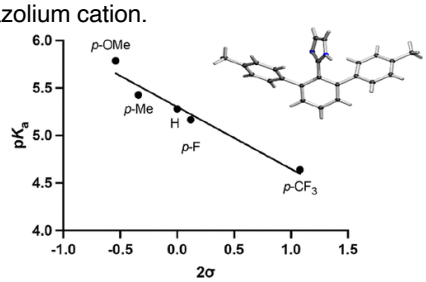
Noncovalent interactions involving aromatic rings are of great importance in both molecular and biological recognition. In particular, quantifying the energetics of intermolecular interactions between aromatic rings and polar functional groups, including the positively charged functionalities (i.e., cation–π interactions), in biology remains a challenge. For such aim, 2,6-diaryl aromatic compounds have been used as particularly suitable model systems for studies of intramolecular polar–π interactions with several functional groups, such as carboxyl, hydroxyl, thiol, silyl, boronic acid, tetrazole, sulfonamide, and various anions and cations. The electronic properties of two flanking rings can be fine-tuned by substituents at the para position.[1] In our most recent work,[2] we analyze the noncovalent interactions between the imidazole ring and other functional groups. We report physical-organic chemistry studies on 2-(2,6-diarylphenyl)-1H-imidazoles and their protonated forms to investigate the noncovalent interactions between the central imidazole ring and two flanking aromatic rings possessing substituents at the para/meta position. Hammett analysis revealed that pKa values and proton affinities correlate well with Hammett σ values of para-substituents at the flanking rings. Additional quantitative Kohn–Sham molecular orbital and energy decomposition analyses reveal that through-space π–π interactions and NH–π interactions contribute to the intramolecular stabilization of the imidazolium cation.



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Oxoammonium salts as mediators in water oxidation

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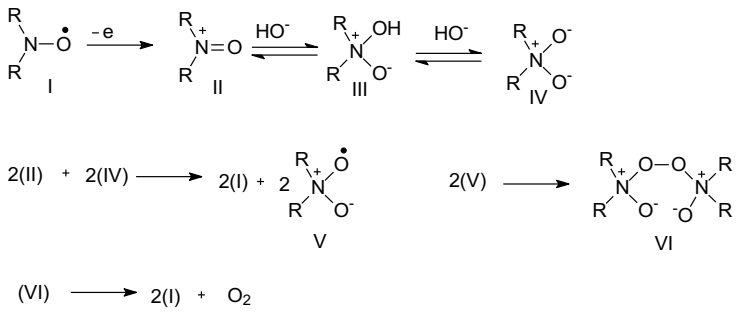
Photochemical and electrochemical oxidation of stable nitroxide radicals (I) both result in formation of oxoammonium cations (II). At alkaline pH values, above pH 9, the (II) is reduced quantitatively to the original (I), with concomitant formation of molecular oxygen. Volumetric and EPR measurements reveal that about *ca.* 1 mole of O_2 is produced per 4 moles of reduced (II). This cycle could be repeated many times. The mechanism for production of oxygen from water in the reaction conditions has not been described before. In this reverse reaction compound (II), with a reduction potential (0.8-1.0 V *vs* NHE), formally oxidizes the OH^- anion, with a very high oxidation potential (2-2.6 V *vs* NHE); thus, the direct oxidation reaction seems to be thermodynamically impossible. A plausible reaction scheme that can resolve this paradox involves reversible addition of OH^- to the (II), and deprotonation of the obtained adduct (III) to (IV) with subsequent oxidation to a free radical intermediate (V). Dimerization of this intermediate (V) produces a peroxide which spontaneously decomposes to molecular oxygen and two molecules of the original compound (I).



EPR experiments, performed in $H_2{}^{17}O$, electrochemical measurements, analysis of the pH-dependence of the reaction, and quantum chemical calculations (B3LYP/6-311+G** using Spartan 20 package) all support the suggested scheme.

Understanding the unexpected selectivity in the Rh(II) Catalyzed C(sp³)-H amination of propylbenzene

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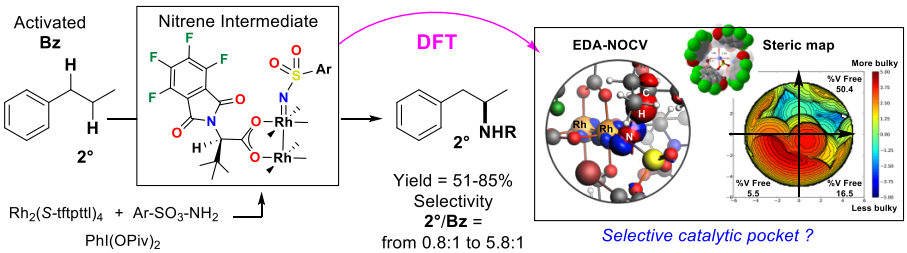

The design of site-selective C–H functionalization reactions is a great challenge with important applications in organic synthesis. Dirhodium(II) complexes are among the best catalysts to perform selective insertion of nitrenes into C(sp³)-H bonds.[1] In this respect, recent experimental results showed a remarkable selectivity for the amination of propylbenzene with the Rh₂(*S*-tfpttl)*4* complex as catalysts.[2] To understand this selectivity, we perform DFT calculation to reveal the factors guiding the catalytic system. Our strategy involves evaluating the mechanism to disclose the electronic or steric factors controlling the selectivity between the secondary (2°) vs benzylic (Bz) C–H bond. In this study, we computed the general mechanism for the functionalization of the C-H bond, which involves either i) a concerted C–H insertion or ii) a stepwise process of hydrogen atom abstraction, followed by radical recombination. The mechanism found computationally indicates that the concerted singlet mechanism was favoured, preferentially occurring at the non-activated 2° position as observed experimentally. We also applied the steric map plot tool to understand the interaction between the catalyst and substrate controlling the selectivity. Our results evidenced the role of the catalysts' pocket in stabilizing key intermediates, and the influence the activations barriers for the C–H amination.

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Intermolecular Covalent Interactions

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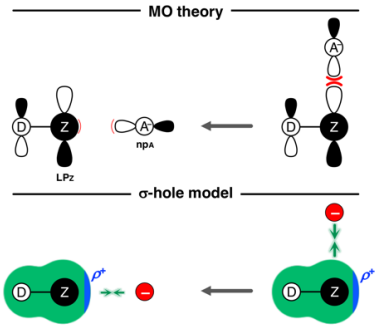
Pnictogen (PnB), chalcogen (ChB), halogen (XB), and hydrogen (HB) bonds are intermolecular interactions of the type $D_mZ\cdots A$, where Z = Pn, Ch, X, H.[1,2] Typically, the s-hole model is invoked to rationalize the unexpected attraction between two partially negatively charged atoms and the geometry of these intermolecular interactions.[3] This model posits that the $D_mZ\cdots A$ complexes are bound and linear due to a Coulombic attraction between a positive electrostatic potential on the molecular surface of the bond donor (D_mZ) and the negative, point charge-like bond acceptor (A). We show how this treatment of atoms and molecules is oversimplified and unphysical.[4] Not the Coulombic interactions, but the steric Pauli repulsion is the driving force preventing the bending of the bond acceptor away from D–Z•••A linearity. In fact, the Coulombic interactions favor (not oppose) bending. The cohesion in these interactions furthermore receives a major contribution from HOMO–LUMO orbital interactions. Therefore, we suggest abandoning the term non-covalent interactions for such bonds and instead using the designation intermolecular covalent interactions (ICI).



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Probing the mechanism of trialkylborane-oxygen radical initiators by trapping radical intermediates

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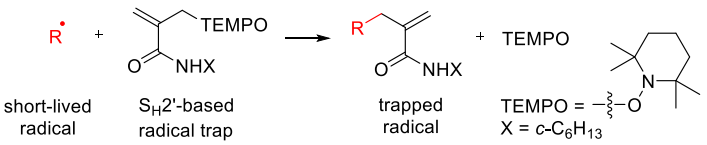
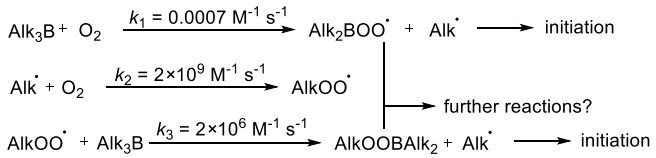
We recently reported a new method for radical trapping based on an S_H2' radical substitution of allyl-TEMPO derivatives.[1] Here, this method is applied to explore the mechanistic details of trialkylborane autoxidation which is a popular method for initiating radical reactions. The autoxidation produces alkyl radicals Alk•,[2] however the side products are boron-containing peroxides with poorly-understood chemistry.[3]

S_H2'-based radical trapping



Trialkylboron-air radical initiator



We monitored trialkylborane reaction with oxygen in the presence of the S_H2' radical trap using ^1H, ^{11}B NMR spectroscopy and mass spectrometry. This made it possible to simultaneously and quantitatively detect starting materials, products and radical intermediates. In addition, we isolated borane peroxides and demonstrated that some of their further reactions proceed *via* a radical mechanism which makes a very significant contribution to the overall radical initiation under commonly-used conditions. We have demonstrated that understanding these reactions makes it possible to initiate radical chain reactions that could not be initiated using standard trialkylborane initiation protocols.

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Kinetics and Mechanism of Azole n-π* Catalysed Acylation

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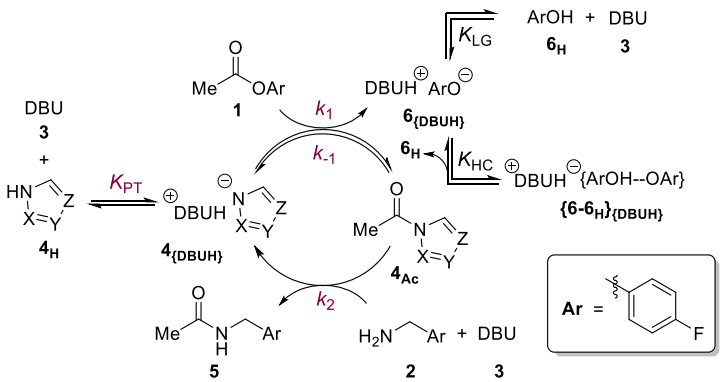
Azole anions are highly competent in the activation of weak acyl donors,[1-2] but, unlike neutral aprotic Lewis bases, they have not yet gained significant traction as acylation catalysts. Curious as to why this should be so, we have investigated the azole-catalyzed aminolysis of *p*-fluorophenyl acetate using *in situ* and stopped-flow $^{1}H/^{19}F$ NMR spectroscopy, multifaceted kinetic analysis, isotopic labelling, ^{1}H DOSY and electronic structure calculations, and used this archetypal system to assemble a holistic mechanistic framework for acylative n-π* catalysis in the anionic mode.[3] Even subtle changes to the solvent, auxiliary base, or azole can elicit profound changes in the temporal evolution, thermal sensitivity and progressive inhibition of azole-catalysed aminolysis, yet we show that these findings can be readily reconciled with a single overarching mechanism – and the general intermediacy of N-acyl azoles. The systematic analysis of 18 azole catalysts, spanning nearly ten orders of magnitude in acidity, highlights the pitfall of pursuing ever-more nucleophilic catalysts without regard for catalyst speciation.



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Methoxylation/Demethoxylation toward anti-Cancer Cephalostatins

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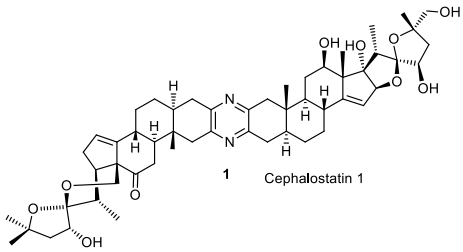
The discovery of cephalostatins (e.g. cephalostatin 1, Fig. 1),[1] a marine natural products which have shown remarkable activity against human cancer cells, attracted us as some groups abroad[3,4] to target the synthesis of such impressive and complicated molecules. We report here the effect of introduction of α-methoxy group to carbonyl group on the biological activities in addition to a mild, efficient and green demethoxylation method after applying regioselective chemical transformations.[4] This work is a part of the progress in desymmetrization of symmetrical bis-steroidal pyrazines (BSPs) (e.g. diketone 2, Fig. 2). Synthesizing a gram-scaled prodrug with potential activity using green methods is our primary target. Scaling up of these methods based on the symmetrical coupling (SC) of two identical steroidal units. The discovery of new green pathways that help in structural reconstruction programming toward the total synthesis of at least one potentially active family member is our secondary target. Our strategy is based on functional group interconversions with high flexibility and brevity using green selective methods. The culmination of our efforts was the effective preparation of anti-cancer prodrug which overcomes cancer-drug resistance (chemoresistance) and has almost no toxicity to the normal cells.



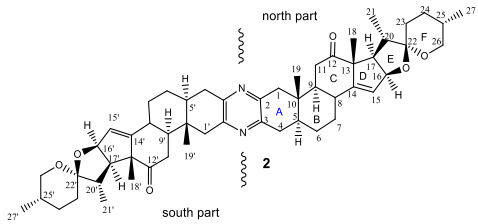


Fig. 1. Structure of cephalostatin 1

Fig. 2. Structure of diketone 2

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Regioselectivity in the Hofmann–Löffler–Freytag Reaction: A Computational Analysis of Rearrangement Reactions

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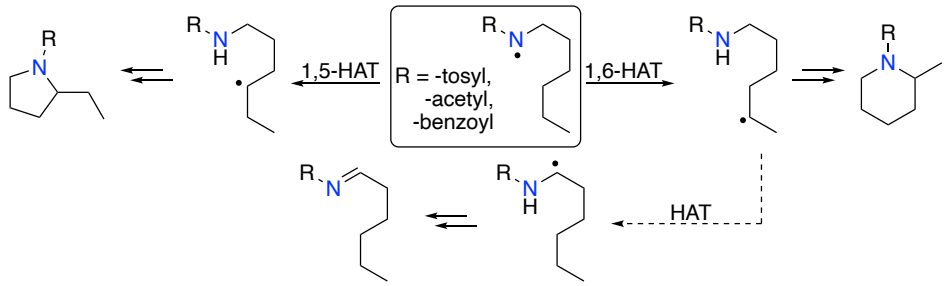
The Hofmann-Löffler-Freytag (HLF) reaction has emerged as a method for the late-stage functionalization of remote C-H bonds,[1] facilitating the synthesis of five-membered pyrrolidine rings through N-centered radicals using a 1,5-hydrogen atom transfer (HAT) process.[2] Notably, the formation of six-membered piperidine heterocycles via 1,6-HAT is prominently observed only within highly rigid or substituted systems.[3]

Our computational studies (RO-B2PLYP/G3MP2large) revealed negligible differences in both thermodynamic and kinetic parameters for the two pathways within unsubstituted alkyl chains. This finding contrasts the experimental dominance of the pyrrolidine ring formation. We delved into the impact of different nitrogen-functionalizing groups, namely tosyl, acetyl, and benzoyl, and probed into both intermolecular and intramolecular mechanisms. Further insights led us to identify other possible rearrangement reactions which likely influence regioselectivity. By harnessing these findings, we can adeptly modify HLF reaction conditions to either favor piperidine outcomes or augment overall yields. Our conclusions were corroborated by EPR and NMR studies on selected systems.



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Mechanistic Studies of Benzylic Oxidation Using Chlorine Dioxide

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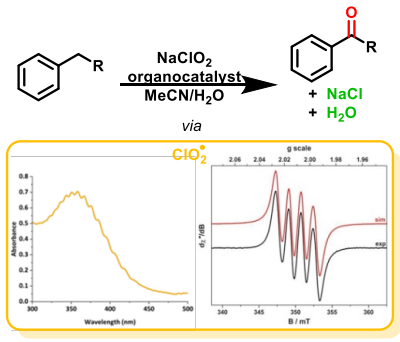
The environmental impact of chemical manufacturing is under growing scrutiny, with stringent regulations on permissible levels of contaminants in industrial effluents.[1] This necessitates innovation in development of new processes which limit environmental disruption.[2] Oxidation chemistry is one area where the development of procedures for scale-up synthesis is challenging. Traditional techniques involve using transition metals, frequently in stoichiometric quantities.[3] This creates issues surrounding waste treatment and removal of metals from final products. Therefore, sustainable alternatives are desirable. Chlorine dioxide has unique properties as a stable radical. It has found extensive use as a bleaching agent in the paper industry and water purification.[4,5] There are isolated examples of chlorine dioxide use in chemical synthesis,[6] however, widespread application is limited by challenges surrounding generation of high-purity chlorine dioxide solutions at synthetically useful concentrations. Oxidation of benzylic methylene positions is possible using sodium chlorite and an organocatalyst.[7] Mechanistic studies have confirmed chlorine dioxide is present under these conditions. Further investigations towards the application of chlorine dioxide in oxidations have been carried out with a view to develop safe, scalable processes with limited environmental impact. This talk will include discussion of mechanistic studies using a combination of *in situ* reaction monitoring, offline measurements and DFT.



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Substituted phenylhydroxycarbenes in the carbonyl-ene reaction in solution

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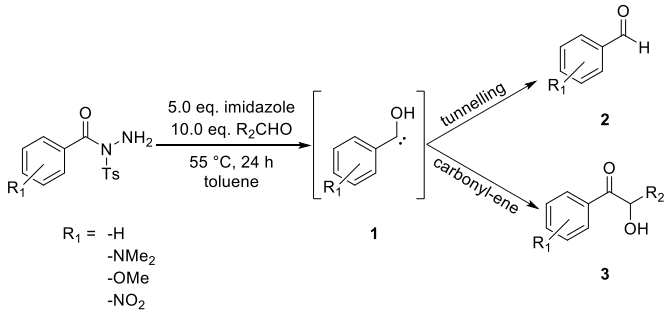
The reactivity of hydroxycarbene (H-C-OH) and other related carbenes has been investigated in-detail under cryogenic matrix-isolation conditions.[1,2] Recently, our group has reported the first evidence for the generation of the phenylhydroxycarbene **1** (R^1 = H) in solution.[3] Apart from the previously reported quantum mechanical [1,2]-H-tunnelling to afford benzaldehyde **2** (R^1 = H),[4] **1** has the propensity to undergo a facile carbonyl-ene reaction with benzaldehyde **2** to afford α-hydroxy ketone **3** (R^1 = H). In this work, we expand these findings and demonstrate that **1** can participate in carbonyl-ene reactions with other substituted benzaldehydes. Furthermore, we demonstrate that alkenes are also capable of undergoing the same reaction with the transient carbene, thus proving that the novel carbonyl-ene reaction is not unique to aldehydes (product formation was in all cases confirmed by NMR and MS). Next, we explored how altering the electronic properties of the reactive carbene can affect the competition between the two pathways. Thus, electron withdrawing and electron donating groups were introduced in the phenyl ring of the intermediate carbene, and their reactivity in the carbonyl-ene reaction was investigated.



Scheme 1. Generation of substituted phenylhydroxycarbenes in solution, and proposed reaction pathways.

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Insights on the structure and photochemistry of synthetic compounds bearing the endoperoxide pharmacophore.

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The pharmaceutical interest in cyclic organic peroxides arises from the 1,2,4-trioxane pharmacophoric moiety of artemisinin, a natural product that integrates the arsenal of frontline antimalarial drugs together with some of its semi-synthetic derivatives (ARTs). Synthetic 1,2,4-trioxolanes and 1,2,4,5-tetraoxanes proved promising alternatives, some exhibiting anti-malarial activity similar or higher than ARTs, even against multi-resistant malaria (e.g. the candidates OZ439 and E209), showing potential for the treatment of other parasitic infections and cancer.[1] Synthetic routes for those classes have been developed and perfectioned.[2] Endoperoxide-based drugs are thought to require bioactivation *via* iron(II)-induced cleavage of the peroxide bond, forming oxygen-centred radicals that rearrange to carbon-centred radicals, these acting through alkylation of parasites' biological targets. To gather further information on the structure, vibrational properties and photoreactivity of trioxolanes and tetraoxanes we investigated two model compounds using the approach depicted in Figure 1.[3,4] Results obtained deepen the knowledge on reactivity and bioactivation mechanisms of those endoperoxide chemotypes.

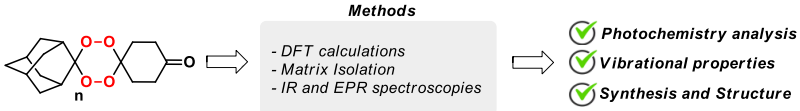

Figure 1. Approach to the study of model. trioxolane and tetraoxane compounds with antiparasitic activity.

We gratefully acknowledge FCT-Portugal for projects UIDB/00313/2020, UIDP/00313/2020, LA/P/0056/2020 (CQC-IMS); UIDB/04326/2020, UIDP/04326/2020, LA/P/0101/2020 (CCMar-CIMAR); and grants SFRH/BD/130407/2017, SFRH/BD/136246/2018, and SFRH/BD/08242/2020.

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Rationalization of Chemical Selectivity in Catalytic Reactions

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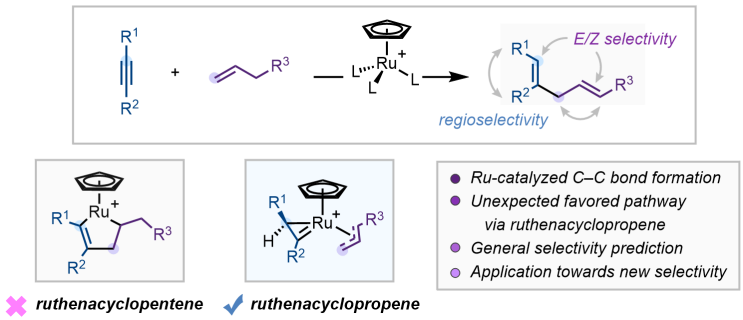
Over the past decades, a large part of organic and organometallic chemistry has involved development and application of new chemical transformations. Understanding reaction mechanisms and chemical reactivity allows us to rationally design and predict novel transformations. A ruthenium-catalyzed Alder-ene reaction of alkenes with alkynes has proved a highly selective and atom economical method for C–C bond formation. The commonly employed mechanism involves the formation of five-membered ruthenacyclopentene intermediates via the oxidative cyclization process.[1],[2] However, selectivities with a certain type of reactants could not be explained with this mechanism, and instead we found that the reaction proceeds through an alternative pathway via the formation of three-membered ruthenacyclopropene intermediates.[3] Our newly proposed mechanism, illustrated with computational and kinetic studies, is able to predict the reactivity and to rationalize the origin of selectivities with a wide variety of reactants. In addition, this simple model was demonstrated to be applicable to an intramolecular cyclization and reactions with more complex reactants.



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A multi-site adsorption model for heterogeneous photocatalysis

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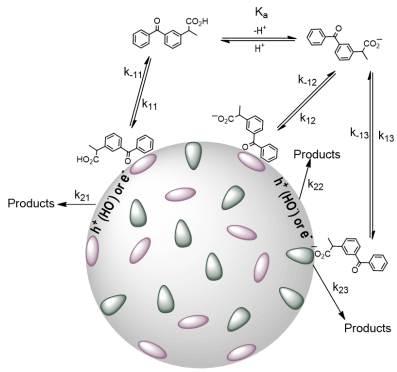
Heterogeneous photocatalysis is a surface adsorption phenomenon. Reagents and photocatalyst are left in contact in the dark for a period, during which adsorption equilibrium is assumed to be reached. But the time to achieve equilibrium may vary. Little is known about how adsorption equilibria are altered by irradiation.

Common interpretation of heterogeneous photocatalysis usually accounts for the first layer of adsorbate, but not beyond. It is reasonable to assume charge carriers migrate beyond the first layer, which needs appropriate modelling. Different adsorption sites may not behave the same, leading to different kinetic behaviour.

A common overlooked problem in heterogeneous photocatalysis is the occurrence of bi-exponential kinetics. Typically, mixing effects or alterations due to irradiation effects are claimed, and the first few points defining the fast initial decay are neglected.

Usually, it is assumed that the surface is homogeneous, with only one type of active adsorption site. A typical organic molecule may offer different possible interactions with the surface. We applied this idea to obtain the kinetic equations.

The Scheme shows this for ketoprofen, a widely used anti-inflammatory. Two different adsorption sites are assumed: interactions through the aromatic ring bearing the benzoyl group and through the carboxylate. There are also three adsorption-desorption equilibria that can be expressed by the ratio of the corresponding adsorption (k_{11}, k_{12}, k_{13}) and desorption rate constants (k_{-11}, k_{-12}, k_{-13}), and need to be considered. Each adsorbate may react with reactive species (h^+, $HO^\bullet$, or e^-), through irreversible steps (k_{21}, k_{22}, k_{23}). Application of our model explains the occurrence of biexponential decays.



Nitrosamine Formation in Pharmaceuticals: Developing Biased Kinetic Models to Assess Nitrosation Risk in Solid Drug Products

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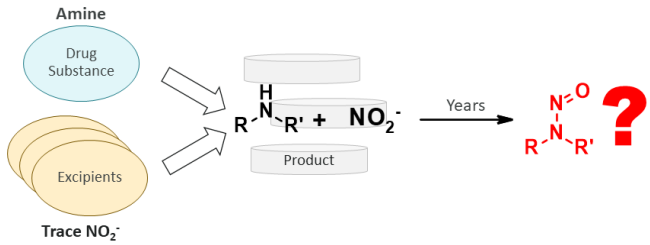
The unexpected finding of nitroso dimethylamine NDMA in valsartan drug substance in 2018 and the subsequent findings of nitrosamines in additional drug products led regulatory agencies to call for pharmaceutical companies to review their products to determine the risk of nitrosamine contamination.[1] After an initial focus on drug substance synthesis, where obvious risks exist, it was found that traces of nitrite present in excipients could react with secondary amines present in solid drug products to form nitrosamines.[2,3] Given that many drug substances are secondary amines or contain secondary amines as specified or trace impurities many drug products could potentially contain nitrosamines.
A biased, predictive model, designed to overestimate the extent of nitrosation based on the published solution phase kinetics of amine nitrosation has been developed.[4,5] The use of some conservative assumptions to enable the extension of this model to consider the nitrosation of an amine occurring within a solid drug product over the product shelf life will be described.



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How the Chalcogen Atom Size Dictates the Hydrogen-Bonding Capability of Amides

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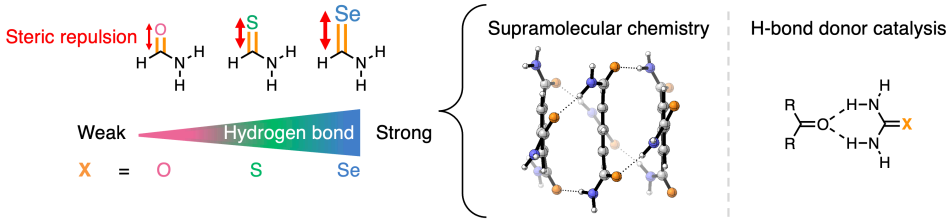
Thio- (X = S) and selenoamides (X = Se) can form stronger hydrogen bonds (H-bonds) than carboxamides (X = O), despite the lower electronegativity of S and Se compared to O. This phenomenon has been experimentally explored, particularly in organocatalysis[1] and supramolecular chemistry,[2] but a sound electronic explanation is lacking. In this talk, I will demonstrate that the NH_2 groups in thio- and selenoamides are more positively charged than in carboxamides, and thus better H-bond donors.[3] Our quantum chemical analyses reveal that this originates from the larger electronic density flow from the nitrogen lone pair of the NH_2 group towards the lower-lying $\pi^*_{C=S}$ and $\pi^*_{C=Se}$ orbitals than to the high-lying $\pi^*_{C=O}$ orbital. The relative energies of the $\pi^*_{C=X}$ levels follow from the mutual π-overlap between the chalcogen *n*p and carbon 2p atomic orbitals, which is set by the carbon–chalcogen equilibrium distance, a consequence of the steric Pauli repulsion between the two bonded atoms. Thus, not the electronegativity nor the often-suggested polarizability but the *steric size* of the chalcogen atom determines the amide's hydrogen-bond donor strength. Finally, I will demonstrate the overlooked role of the chalcogen atom size on the suitability of the molecular geometry for intermolecular H-bonding.[4]



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Fundamentalist vs. Canonical Descriptions of Isotope Effects in Enzymic Reactivity

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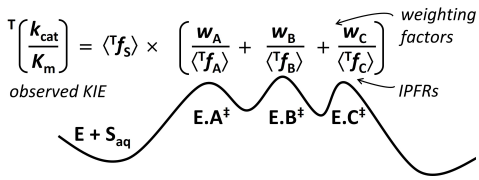
Kinetic isotope effects (KIEs) provide a powerful experimental probe for enzyme mechanisms provided that observed ratios of rate constants (upon k_{cat}/K_m for competitive reactions where the reactant state is the free substrate in solution) may be interpreted reliably. The traditional ("canonical") approach to analysis of mechanisms with multiple reaction steps in series involves consideration of "commitments to catalysis" for each step and which often leads to extremely complicated expressions for observed isotope effects in terms of individual steps;[1] practical solutions usually require the making of assumptions and simplifications that may not always be valid. Computational simulation is now capable of yielding valuable insight, complementary to experiment, including isotopic partition-function ratios (IPFRs)[2] for minima and saddle points on a potential-energy surface, corresponding to intermediates and transition states[3] on a Gibbs-energy surface for the enzymic reaction. Following Schowen's "fundamentalist" approach to enzymic catalysis,[4] we present a treatment of KIEs for multistep enzymic reactions that avoids the use of commitment factors or consideration of intermediates but focuses solely on the relative contributions of transition states in series. Accordingly, computed IPFRs should be combined to yield an overall KIE directly for comparison with an observed KIE rather than with derived "intrinsic" KIEs.



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Uncertainty quantification of organic reactivity

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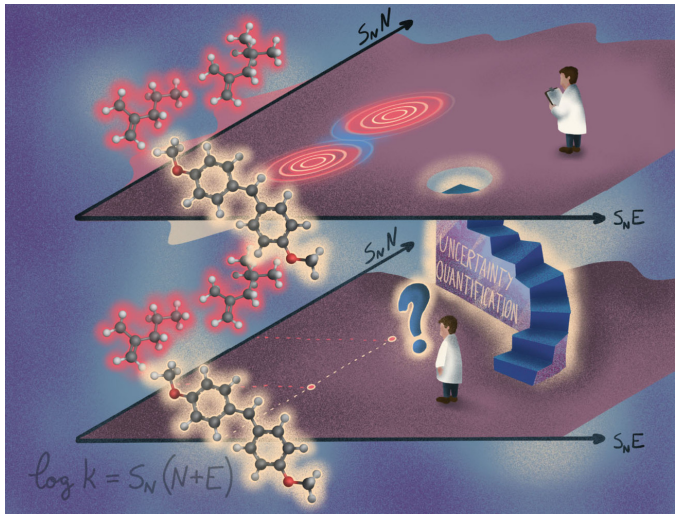
Polar organic synthesis can be rationalized by Mayr's empirical relationship linking bimolecular rate constants to only three reactivity parameters. Here, we propose an extension to his reactivity approach that is rooted in uncertainty quantification.[1] Most importantly, it yields uncertainty estimates for bimolecular rate constants. Synthetic chemists can exploit these virtual error bars to make synthesis planning more reliable. Computational chemists, in turn, can take advantage of the new approach by creating low-cost pseudo-benchmarks to diversify test sets for model evaluation. Currently, we study how organic reactivity can be determined more efficiently by a combination of quantum chemistry and machine learning.[2] We are particularly interested in real-time reactivity prediction.[3]



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Enhancing Organic Chemistry With Calculations: From Density Functional Theory to Machine Learning

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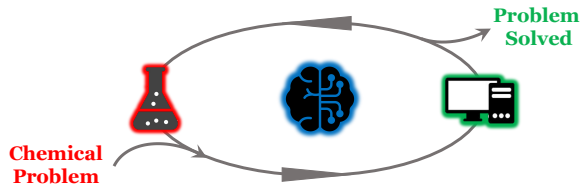
Recent developments in quantum chemistry and computational methods empower us to comprehensively grasp and predict the outcomes of organic reactions. We showcase the effectiveness of synergizing experimental findings with theoretical understanding, exemplified through recent cases.

For various organic transformations, e.g., modern catalytic Claisen-type rearrangements,[1] we not only elucidate experimental observations but also predict more efficient reaction pathways. Successfully applying density functional theory (DFT) for a major part of our studies, yet we were able to identify significant limitations in comparison to wave function-based methods for certain systems. We propose alternative strategies to tackle these chemical challenges. Additionally, we present an innovative approach to interpreting yields on an example of the Buchwald-Hartwig amination via statistical analysis as a step towards precise reactivity predictions aligned with the principles of modern data-driven chemistry.[2]

Overall, we introduce iterative cyclic strategy calculations/experiments/calculations for engineering organic reactions. Our computational investigations offer explanations for experimentally observed phenomena while providing new insights for subsequent experiments and computations.



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Computational framework for automated discovery of degradation reaction mechanisms of organic redox flow battery materials

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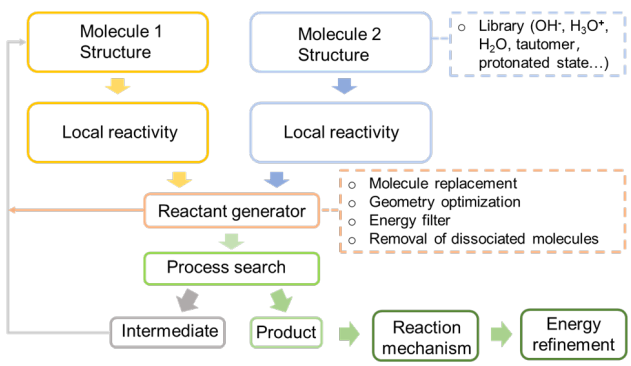
Organic redox flow batteries (ORFBs) show great potential for large-scale energy storage. The key performance indicators are the redox potentials of the redox couples, solubility in the solvent of choice, and their (electro)chemical stability. The latter requirement is currently the main factor preventing the deployment of ORFBs.

The undesired parasitic reactions are known for some types of electrolytes, while for newly developed materials, they often are not. There are few mitigation strategies to improve the stability of ORFB electrolytes without sacrificing other properties. Being able to predict possible degradation reactions and estimate their rates under operating conditions would open a possibility for the systematic and rational design of new stable electrolytes.

In this contribution, we will present a computational framework whose objective is to map out the degradation network and estimate the thermodynamic and kinetic stability of the material with minimal a priori knowledge. The framework is based on a potential energy surface exploration algorithm that combines electronic structure and atomistic simulation methods like DFTB, DFT, implicit solvent models, and single-ended transition-state optimization algorithms. We will demonstrate the assumptions and working principles and illustrate the performance with a few experimentally validated degradation mechanisms.



Posters

Detection of Palladium(II) Ions and Its Application in Live Cell Imaging

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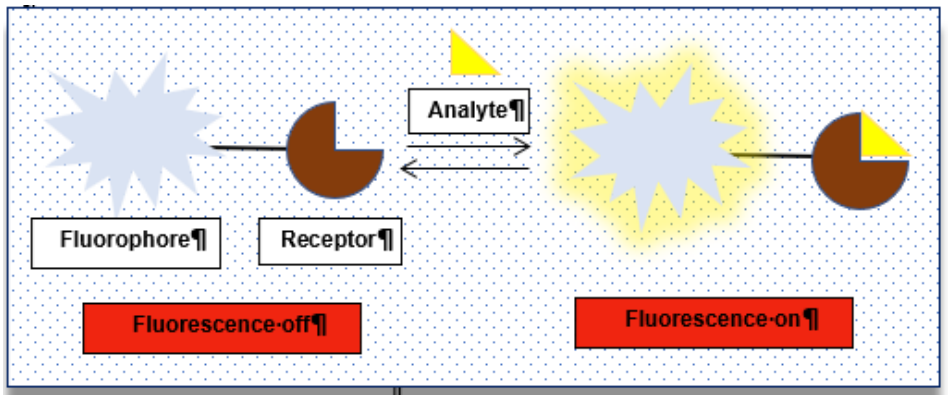
The use of dyes bearing fluorescent properties is gradually becoming more common in various fields of science, especially in chemistry, biology, and medicine. In recent years, chemosensors have become important alternatives to classical analytical methods due to their high analyte selectivity and sensitivity, ease of applicability, and reproducibility. [1]

Palladium (Pd) is an important transition metal that belongs to the platinum group. Its complexes are widely used in modern synthetic chemistry, materials science, and pharmaceutical chemistry. However, the massive global usage of palladium has led to several pollution and health-related problems. [1] For example, it can bind to various biomolecules including proteins, and DNA or RNA, and interfere with various biological processes. Thus, it is crucial to develop new analytical tools to monitor the presence of palladium ions in aqueous solutions and biological systems. [2]

Herein, we developed a new turn-on probe based on the BODIPY scaffold, BDP-Pd, for selective and sensitive detection of Pd2+ ions. The coordination of Pd2+ ions to the receptor unit enhances the fluorescence emission of the probe via the inhibition of the PET mechanism. Moreover, the designed probe allowed us to monitor trace palladium in cellular media.



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Electric field-induced reactivity and selectivity: Insights from chemical bonding analysis

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Electric fields (EF) can induce substantial changes in reaction rates, the selectivity towards a particular product, or in general to reaction mechanisms, even for the simplest transformations. This bears tremendous potential impact on various areas of catalysis, ranging from heterogeneous to enzymatic catalysis. The analysis and understanding of such effects at the molecular level is crucial for the design of novel processes and optimization of the existing ones.[1,2] To this end, the activation strain model and the energy decomposition analysis (EDA) are suitable computational techniques, however they are computationally demanding.[2,3] Herein, we present a fast and efficient methodology to decompose energy differences (kinetics and thermodynamics) into physically meaningful energy terms in the presence of an EF in any direction of the space: the Field-Dependent Barrier Activation Strain Model (FDB-ASM) and Field-Dependent Barrier Energy Decomposition Analysis (FDB-EDA).[3] Analysis and visual representations of the electric-field effects on reactivity and selectivity will be presented.

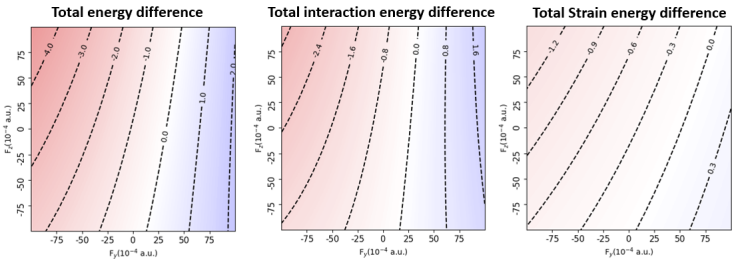

Figure 1. FDB-ASM analysis of the *endo* vs *exo* selectivity of a simple Diels-Alder reaction.

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1,3-Dipolar Cycloaddition: From Conception to Quantum Chemical Design

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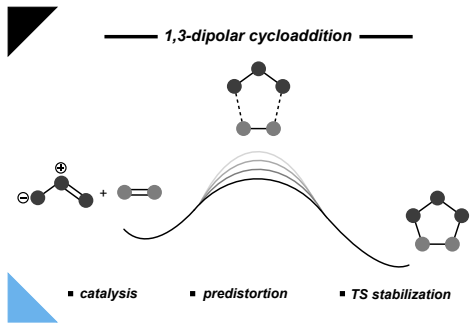
The 1,3-dipolar cycloaddition (1,3-DCA) reaction, conceptualized by Rolf Huisgen in 1960, has proven immensely useful in organic, material, and biological chemistry. Additionally, the 1,3-DCA has played a key role in the emergence of bioorthogonal chemistry.[1] These reactions can be promoted, either by predistortion or electronic tuning, so that they go with much higher reactivity, selectivity, and yields, often at ambient temperatures. *In silico*-derived design principles have proven invaluable for the design of new dipolarophiles with tailored reactivity. We will discuss everything from the conception of the 1,3-DCA all the way to the state-of-the-art methods and models used for the quantum chemical design of novel reagents.[2]



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Vinyl Esters of alpha-Ketocarboxylic Acids for Parahydrogen-Enhanced Metabolic Spectroscopy and Imaging

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Hyperpolarization is an effective approach to boost the MRI signal by a factor of 10^4 to 10^6. The improvement in sensitivity enables detection of non-hydrogen nuclei in real time at low magnetic field strengths. Small molecules such as pyruvate are ideal candidates for a novel class of hyperpolarized MRI contrast agents that can visualize the metabolism of the body and thus contribute to the early detection of cancerogenic metabolic changes, long before pathologies manifest and treatment becomes challenging. [1][2]
Dissolution dynamic nuclear polarization (dDNP) is arguably the most widely applied method for hyperpolarization, however, it is complex, slow, and expensive, while the availability of precursors often limit the more cost efficient and faster parahydrogen-based alternatives.[3] Here, we report the synthesis for novel ^{13}C, deuterated ketocarboxylic acids, and a much-improved synthesis of 1-^{13}C-vinyl pyruvate-d6, arguably the most promising tracer for hyperpolarizing pyruvate using parahydrogen induced hyperpolarization by side arm hydrogenation (PHIP-SAH).[1][4] The method is very versatile, the sidearm can be easily deuterated and the yield is at least 8 times higher than competing approaches. [4]

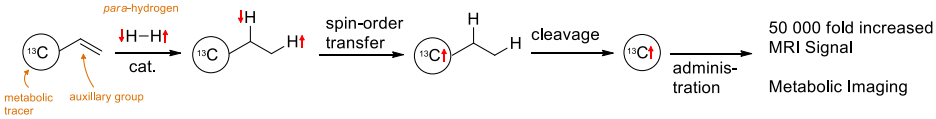

Figure 1: PHIP SAH process to get a hyperpolarized MRI signal of a small molecule.

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Highly Sensitive, Easy-to-Use, One-Step Detection of Peroxide-, Nitrate and Chlorate-Based Explosives

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The rising misuse of homemade explosives, like peroxides, nitrates, and chlorates, by terrorists, criminals, and amateur chemists is a concerning trend. These substances are easily obtained, with instructions available on the internet.[1,2] Detecting them swiftly and at low concentrations is crucial for safety. Current methods often involve sophisticated, electrically operated, analytical equipment and multiple steps.[3] Our solution employs a one-step porphyrin-based approach, akin to a pH test strip, for user-friendly handling. Notably, our method detects the peroxide-based explosive TATP, frequently employed by terrorists, at a sensitivity of 40 ng. This enables non-contact gas-phase detection, indicated by a color change from red to green (formation of a π-radical cation). Additionally, nitrates and chlorates like ammonium nitrate, urea nitrate, and potassium chlorate are directly detected upon contact, with sensitivity ranging from 85 to 350 ng. This is evidenced by a color change from red to dark brown (formation of a dication). The test thus detects all home-made explosives and distinguishes between the extremely impact, shock and friction sensitive peroxides and the less sensitive nitrates and chlorates by color change of a simple test strip.

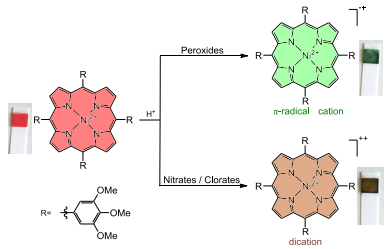

Figure 1: Overview for the detection of peroxide (color change from red to green) and nitrate-based (color change from red to brown) explosives.

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Multiple Functionalized Diazocines for Hybrid Smart Materials

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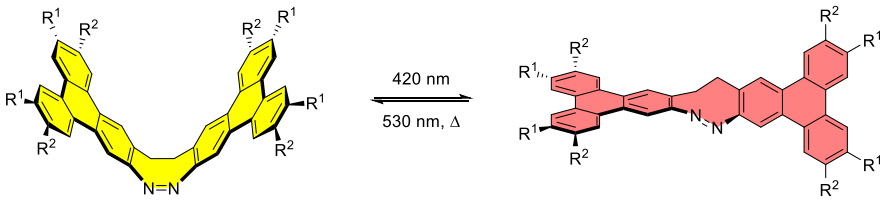
Since 2009 at the latest, bridged azobenzenes, so-called diazocines, have been very well studied as photoswitches and their photophysical properties are several times superior to those of their non-bridged analogues.[1] The application of diazocines in photoresponsive hybrid smart materials is therefore a logical next step, which is, however, often limited by the lack of easy accessibility of sufficiently appropriate derivatives.[2,3,4,5] For this purpose, we report the synthesis of two different novel classes of diazocines (bistriphenylene diazocines as well as imide diazocines) with multiple substituted extended aromatic π-systems. Depending on the required field of application, these diazocines can be late stage derivatized for photochromic liquid crystalline and mechanophoric behavior as well as for incorporation as cross linkers in aerogel actuators and gradient copolymers accessible through initiated chemical vapour deposition (iCVD). These compounds convince by their mechanomolecular properties (e.g. greater amplitude of motion during isomerization of the azo group, multiple symmetric binding sites, better force transmission to the molecular periphery), which makes them suitable universal compounds for use in novel photoresponsive hybrid smart materials such as in soft robotics.



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Reactivity of functionalized silica surfaces with ozone and hydroxyl radicals

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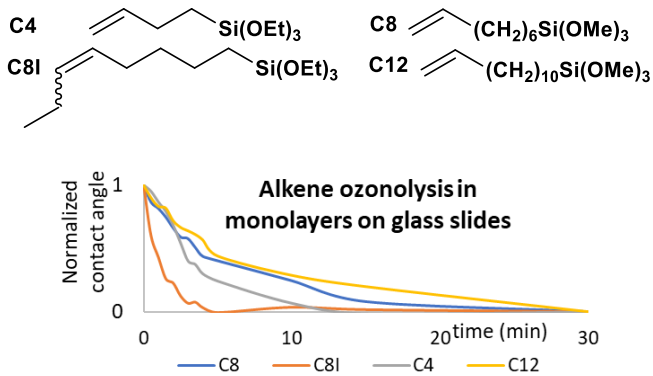
Understanding chemical reactivity of surface-attached functional groups with gaseous reactive species is critical for many applications including atmospheric chemistry, paints/coatings and sensors.[2] As contributors to the RADICAL consortium working on atmospheric radical sensors,[1] we have studied reactions of ozone and non-thermal $He/H_2O/O_2$ plasma (as a source of hydroxyl radicals) with functionalized self-assembled monolayers on non-porous silica nanoparticles and planar silica substrates. In order to characterize the reaction products on silica nanoparticles, we have developed methodology for removing the monolayer from the surface to yield soluble products that can be analysed by conventional analytical techniques.



We are particularly interested in the effect of monolayer environment (e.g., the presence of adjacent molecules, monolayer thickness, position of the functional group in the monolayer) on the kinetics and chemical reactivity of the monolayers. Initial results suggest that the reactivity follows a similar trend to the bulk condensed phases with higher ozone reactivity for shorter monolayers.

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Kinetics and Mechanism of Azole n-π* Catalysed Acylation

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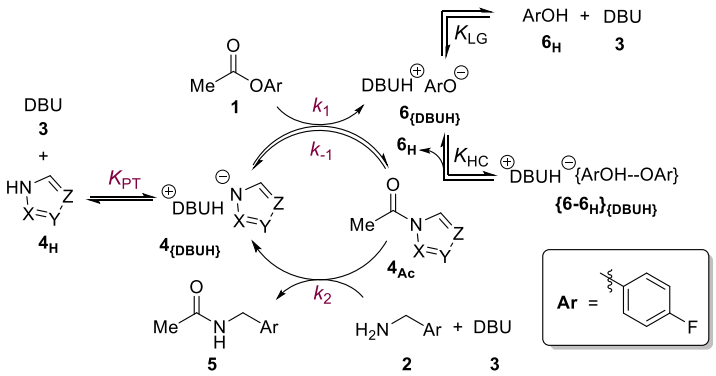
Azole anions are highly competent in the activation of weak acyl donors,[1-2] but, unlike neutral aprotic Lewis bases, they have not yet gained significant traction as acylation catalysts. Curious as to why this should be so, we have investigated the azole-catalyzed aminolysis of *p*-fluorophenyl acetate using *in situ* and stopped-flow $^{1}H/^{19}F$ NMR spectroscopy, multifaceted kinetic analysis, isotopic labelling, ^{1}H DOSY and electronic structure calculations, and used this archetypal system to assemble a holistic mechanistic framework for acylative n-π* catalysis in the anionic mode.[3] Even subtle changes to the solvent, auxiliary base, or azole can elicit profound changes in the temporal evolution, thermal sensitivity and progressive inhibition of azole-catalysed aminolysis, yet we show that these findings can be readily reconciled with a single overarching mechanism – and the general intermediacy of N-acyl azoles. The systematic analysis of 18 azole catalysts, spanning nearly ten orders of magnitude in acidity, highlights the pitfall of pursuing ever-more nucleophilic catalysts without regard for catalyst speciation.



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The Enol of Propionic acid

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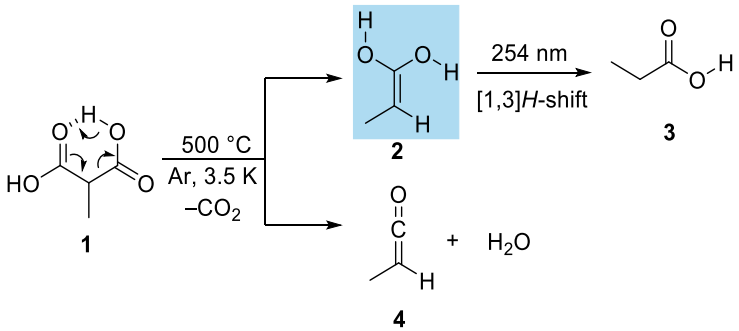
We demonstrate the gas-phase synthesis of prop-1-ene-1,1-diol **2**, the hitherto unreported higher energy tautomer of propionic acid, *via* flash vacuum pyrolysis of methylmalonic acid **1**. The pyrolysis products were trapped in an argon matrix at 3.5 K and were characterized by IR and UV-Vis spectroscopy in combination with density functional theory computations at the B3LYP/def2-TZVP level of theory. Upon photolysis at λ = 254 nm, enol **2** rearranges to propionic acid **3**. This is significant in low-temperature environments, such as extraterrestrial space, where temperatures are generally too low to overcome the necessary activation barriers. Enol chemistry including **2** has been suggested to have played an important role in the chemical evolution that led to the origin of life on Earth.[1] One possibility is that enols have reached Earth through meteorites and have given rise to higher molecular weight follow-up compounds that played a role on prebiotic Earth.[1-4] Enediol **2** is expected to form *via* a similar mechanism as demonstrated for the preparation of the enediol of acetic acid, which had been prepared only in 2020.[5]



Scheme 2: 1-Propane-1,1-diol (**2**) generated from methylmalonic acid (**1**) through pyrolysis and trapping in an argon matrix. Subsequent photorearrangement to propionic acid (**3**) or methylketene (**4**).

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tangential-radial Isomerization of Liquid-Crystalline Tristriazolotriazines

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The threefold Huisgen reaction[1] of cyanuric chloride and alkoxyphenyl tetrazoles gives tristriazolotriazines **1a-h**, fluorescent π-conjugated molecules. The phenyl rings are tangentially attached tristriazolotriazine, the torsion angles between triazole and phenyl are 12 – 82°,[2] giving a paddle-wheel structure to these discotic molecules. Triphenyl-TTT melts above 300 °C, but 2 or 3 medium length alkoxy chains result in broad mesophases, typically with a hexagonal columnar structure[3, 4] and often a complex superstructure.[5] Contrary to earlier reports,[3] these DLCs are not thermostable. A rearrangement of the TTT occurs in three successive steps, bringing phenyl substituents from tangential positions in **1** to radial positions as in **2**. The new *r*-TTT is nearly planar, dihedral angles are 6° or less. The extension of the molecular diameter and the planarization have a huge impact on the thermotropic properties: higher melting points are typical, complete destruction of mesomorphism, but also the transformation of non-mesomorphous *t*-TTTs to discotic liquid crystals have been observed.

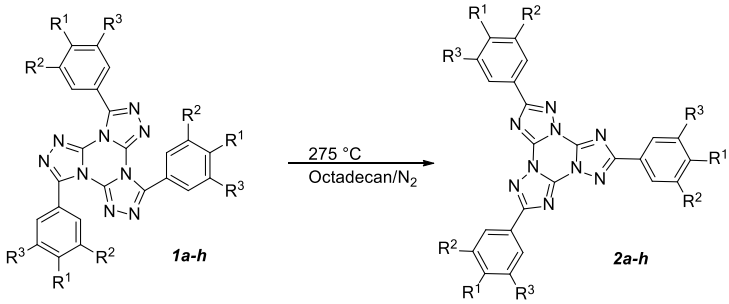

Fig. 1: *Thermal tangential-radial isomerisation of tristriazolotriazines*

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Electrophilic Reactivity of Cyclopropanes

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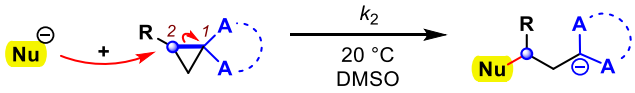
Cyclopropanes react as electrophiles in polar reactions when substituted with electron-accepting groups.[1] A donor substituent at C2 induces strong polarization of the C1–C2 bond, enhancing reactivity toward nucleophiles and steering regioselectivity.[2] Herein, kinetic studies are discussed which provide insights into the factors that control polar cyclopropane reactivity.



A: acceptor group (ester, nitrile, sulfonyl, ...)
R = H, aryl, alkyl

Whereas reactivities of sp^2-hybridized centers (Michael acceptors, carbocations) are fairly well understood,[3] this is not the case for S_N2-type reactions involving sp^3-hybridized carbon centers. Intrinsic properties of the electrophile play an important role and a systematic description of reactivities is difficult due to the concurrent cleavage and formation of a σ-bond. By monitoring non-catalytic ring-opening reactions with strong nucleophiles, inherent reactivities of cyclopropanes can be assessed.[4,5] Cyclopropanes with substituents at C2 react faster than unsubstituted analogues. Variation of substituents at the aryl groups at C2 gives rise to parabolic Hammett relationships. If conformational flexibility of A at C1 is not locked (e.g. by incorporation into a spirocycle) dramatically reduced reaction rates are observed. Rate constants k_2 for ring-opening reactions are compared to related Michael additions and classical S_N2 reactions. Furthermore, quantum-chemical calculations are used to rationalize observed trends.

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Frustrated Lewis Pairs: An efficient and controllable carbon dioxide capture and activation

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Since their discovery in 2006 by Stefan et al. [1], Frustrated Lewis Pairs (FLP) gained a lot of interest in the scientific community due to their large range of applications. The main property that gives a bright future to those systems is their metal-free character that integrates them in the "green chemistry" tendency. Due to the constant growing of CO_2 concentration in the atmosphere one possible application of the FLP is the capture and activation of CO_2 molecules. FLP can be used as a possible storage supply, as well as a catalyst that enables to capture CO_2 and to activate it, making its transformation easier [2]. In the literature, there is a plethora of FLP. From the original $P(^tBu)_3/B(C_6F_5)_3$ [1], to the 5,10-Disubstituted dibenzophosphaborines [3], passing by the $R_3P\text{-}CH_2CH_2\text{-}BR_2$ linked FLP [4], the boron Lewis acid seems to be a very interesting candidate. During the study of several FLP reacting with CO_2 [3-5], it was shown that the capture of carbon dioxide molecules by FLP can be controlled by playing with the acidity and basicity of the Lewis acid and base or by imposing an internal or external electric field. One can pass from a non-favorable, to a thermodynamically favorable reaction.

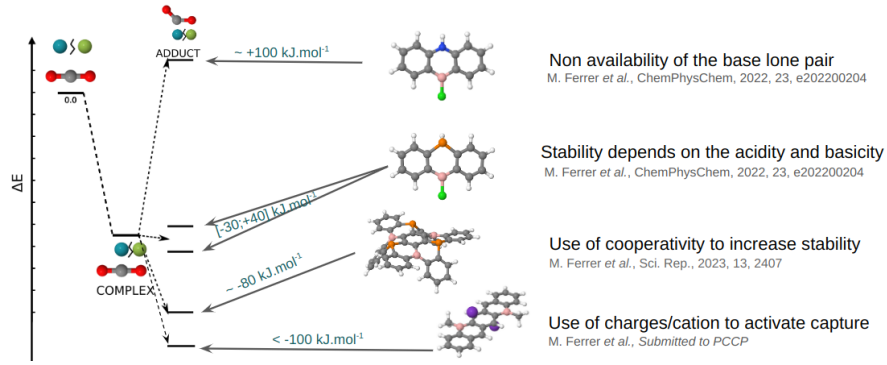

Figure 1: Factors influencing the stability of the adduct formed by an FLP.

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A DFT Study of Isothiourea-Catalysed Diastereoselective Michael Addition of β-Ketoesters to α,β-Unsaturated Esters

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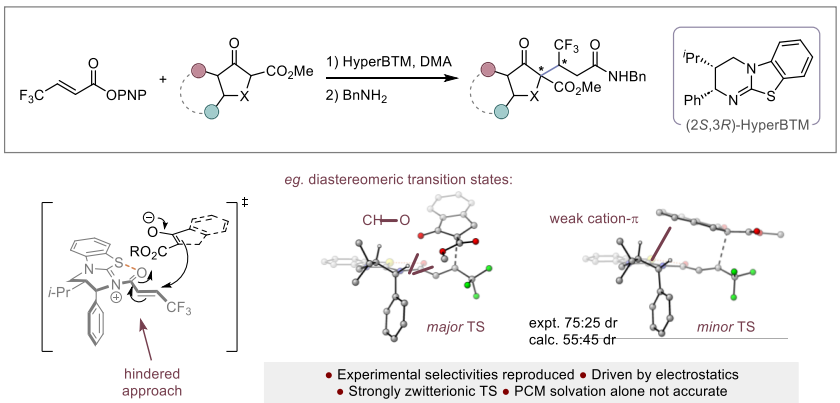
Asymmetric Michael additions are a useful synthetic tool for stereoselective C–C bond formation and have been used previously for the enantioselective addition of malonates to α,β-unsaturated esters.[1] Isothiourea organocatalysts have been used to promote facial selectivity of such conjugate addition reactions by hinderance of one face by the phenyl directing group, locking the unsaturated ester orientation by means of a 1,5-S···O chalcogen interaction.[2]

In this work, we use DFT (M06-2X$_{SMD}$/def2-TZVP//M06-2X$_{SMD}$/def2-SVP) to rationalise the diastereoselectivity achieved in the reaction using the Lewis basic isothiourea, HyperBTM, as a catalyst. Due to the strongly zwitterionic character of the stereodefining transition state, careful selection of the solvent model was important to identify the correct *major* diastereomer. Explicit solvent molecules were found to improve the description of the interaction between the solute and solvent, with electrostatics playing a key role in controlling the diastereoselectivity.



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ESOR2023
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Electrophilic Reactivities of ortho-Quinone Methides

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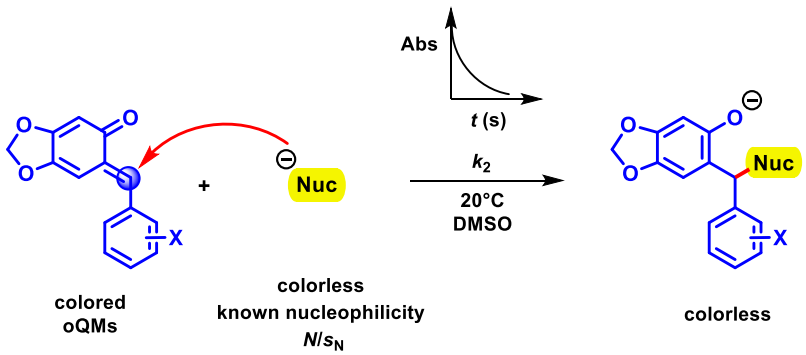
Ortho-quinone methides (oQMs) are highly versatile reagents which are frequently used in organic synthesis. For example in various (4+n) cyclization reactions they generate useful heterocycles like the chromane or chromene motifs.[1-4]

We now synthesized a series of stable oQMs and characterized their electrophilic reactivities by photometrically following the kinetics of their reactions with carbanions in DMSO at 20°C. The experimental second-order rate constants k_2 were evaluated by the linear free energy relationship lg $k_2 = s_N(N + E)$[5] and used to determine the electrophilicity descriptor E of the oQMs. The thus determined E parameters were then successfully utilized to predict novel oQM reactions with further types of nucleophiles.

The electrophilicities E of oQMs correlate linearly with quantum chemically calculated methyl anion affinities (MAAs), frontier orbital properties, Hammett substituent constants and experimentally determined reduction potentials E_p^{red}. These correlations will be useful to tailor novel oQMs with predictable properties and to compare them to previously characterized pQMs.[6]



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Azo Based Ni(II)-Porphyrin Derivatives as Switchable MRI Contrast Agent

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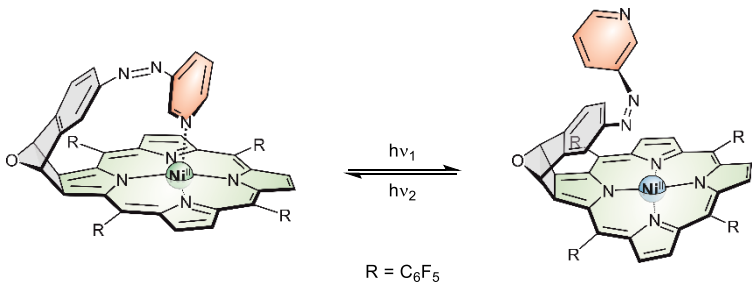
Traditional methods for functional contrast agents often focus on regulating water exchange in paramagnetic gadolinium complexes. In contrast, our approach centers on manipulating the spin state of a transition metal ion. While Gd3+ complex relaxivity is never fully silenced even in tight ligand cages due to outer sphere and spatial effects, transitioning a transition metal complex to the singlet spin state renders it completely silent under MRI. This makes our approach more efficient in switching.

However, the drawback is that gadolinium(III) boasts the highest relaxivity among all elements on the periodic table. Opting for a different metal sacrifices sensitivity. Yet, toggling contrast multiple times might offset this with enhanced signal-to-noise ratios compensating for lower relaxivity.

Our method employs a porphyrin-based structure that complexes a nickel(II) ion within. A covalently linked azo-pyridine can reversibly isomerize upon light irradiation, coordinating with the nickel center, shifting the nickel ion to a square pyramidal coordination, inducing a paramagnetic high-spin state.

DFT calculations demonstrated that a chlorine framework in the cis-isomer provides nearly optimal binding conditions. Introducing the azo function through cycloaddition also converts the porphyrin framework into a chlorin structure.



Pharmacophore-based virtual screening for new modulators of RORγ

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Between 17 and 32 % of adults in Europe[1] suffer from diseases related to the metabolic syndrome. These diseases include diabetes[2] but also cardiovascular diseases[2]. Because of their high prevalence, the development of new drugs for treating such conditions is particularly relevant. One target associated with metabolic syndrome-related diseases is the RAR-related orphan receptor gamma (RORγ)[3]. In order to identify new bioactive substances that intervene with RORγ, pharmacophore models were developed for virtual screening. The best-performing pharmacophore model obtained good early enrichment (EF1%) on a test set of 1149 known RORγ modulators and 306 confirmed inactive compounds. From the Enamine HTS collection database, eight compounds were selected and purchased for experimental testing. One of these compounds was confirmed to inhibit RORγ with an IC50 of 2.3 µM. With a maximum similarity of 0.34 to known actives and a maximum similarity of 0.30 to known inactives of RORγ, the hit can be considered to be innovative.

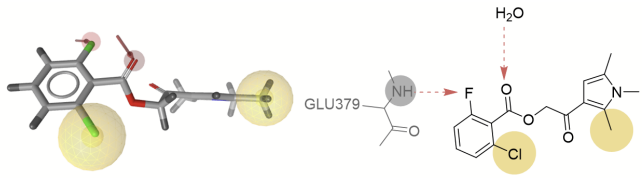

Figure 1: Hit structure for RORγ with the corresponding pharmacophore model in the 3D representation (left) and the 2D representation (right).

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Rhodanine-based Chromophores – Photoswitching and Light-triggered Apoptosis

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[a] Friedrich-Alexander-Universität, Erlangen-Nürnberg, Germany
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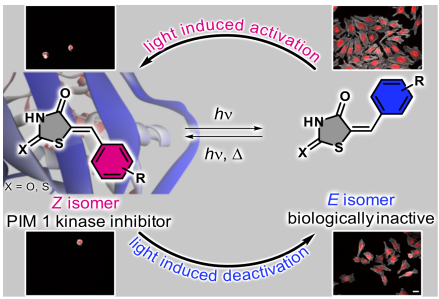

Molecular photoswitches are compounds that can adopt two or more reversible states under external, waste-free stimuli. A structural change is often accompanied by a modification of the physical or biological properties, making molecular photoswitches attractive for a wide range of applications. Nevertheless, obtaining simple and efficient access to these molecular tools is usually not granted, requiring intricate syntheses and substitution schemes to achieve effective photoswitching properties. Rhodanine-based photoswitches are easily accessible in one simple synthetic step without requiring elaborate purification. These photoswitches show great performance as their photoswitching is induced by UV/ vis light in both switching directions. Their high thermal stabilities, high quantum yields together with their ability to form hydrogen bonds allow applications in supramolecular or medicinal chemistry. The known rhodanine-based inhibitor SMI-16a shows light triggered apoptosis as its activity can be switched ON or OFF by reversible photoisomerization between the inactive *E* and the active *Z* isomer. Therefore, rhodanine-based photoswitches represent an easy to access and highly valuable molecular toolbox for implementing light responsiveness to functional molecular systems.[1]

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Molecular Flip Flops: Spin Switching by Intramolecular Feedback

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In this work, a novel spin switch based on a nickel(II) porphyrin is further developed and synthesized to be used as a basic building block for molecular spintronics.
The hairclip porphyrin was developed in our group and is characterized by the fact that it does not contain a photochromic unit, as many other molecular switches do, but the spin state is influenced by an intramolecular cooperative effect. The spin state was combined with the porphyrin conformation and coordination of axial ligands in such a way that the molecules can assume only two states (low-spin/ruffled/decoordinated or high-spin/planar/coordinated). Low-temperature scanning tunneling microscopy was used to demonstrate the selective and reversible switching of individual spin switches using a tunneling current from the STM tip on a silver(111) surface. Both states are stable for at least several days at 4 K.[1]
The new hairclip porphyrin is thus an excellent building block for molecular spintronics, since only one molecule is needed to achieve bistability. Logical units can be generated by covalently linking the individual spin switches.

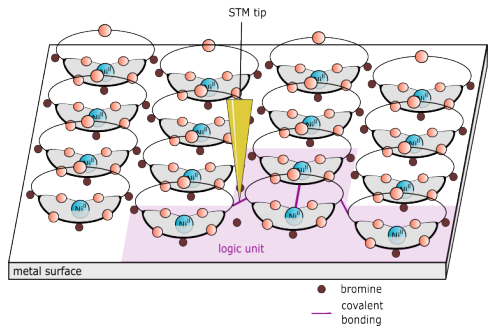

Figure 1: *In situ* synthesis of logic units by Ullmann coupling on a metal surface. The coupling of bromine-substituted hairclip porphyrins can be selectively achieved by excitation with a tunneling current pulse.

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Salts, Hydrates and Homoconjugates in the Direct Formation of Amides

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Amide synthesis is the most frequently used chemical transformation in medicinal chemistry. It is commonly thought that you cannot prepare an amide directly from a carboxylic acid and amine due to formation of an unreactive salt pair. Alternative methods include pre-activation of the carboxylic acid, or addition of catalysts, but this can be expensive and produces a large amount of undesirable waste. Despite the misconception, previous reports have shown that certain combinations of carboxylic acids and amines can react in the absence of additives. [1] The direct coupling route poses a much simpler, atomically efficient route, with water being the only by-product. Mechanistic studies into this direct reaction in the absence of a catalyst remain extremely scarce and inconclusive. In this work, we developed a system which facilitates *in-situ* ^{19}F-NMR reaction monitoring of the non-catalysed direct amide formation without water removal. [2] Analysis of kinetic data in varying reaction conditions, with the support of NMR titrations, revealed the important role of excess carboxylic acid and water in the overall reaction rate. A mechanistic hypothesis was proposed which includes complex equilibria between multiple species to dictate the overall reaction outcome.

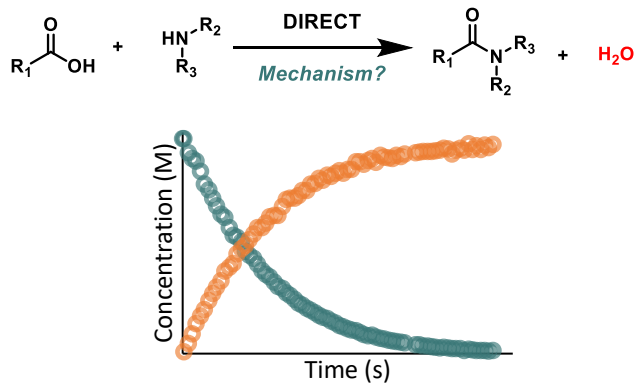

Figure 1. Monitoring reaction kinetics of the direct amide formation using *in situ* ^{19}F-NMR.

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KINETICS AND MECHANISM OF TITANOCENE MEDIATED POLYSULFANATIONS

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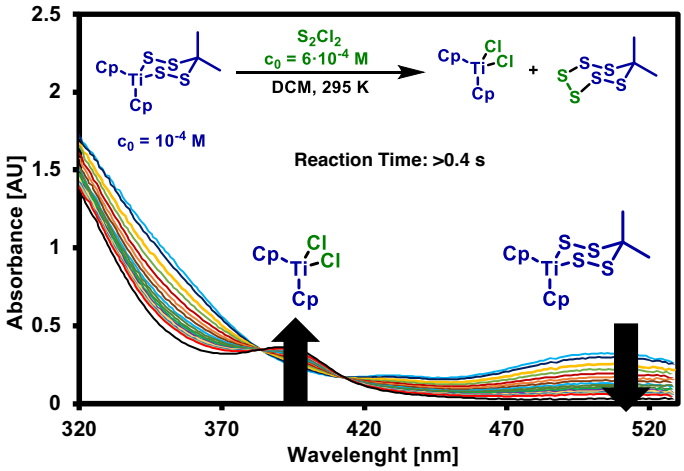
Polysulfanes ($R_1S_xR_2$) have differing properties based on their number of sulfur atoms. Their biological role in the release of hydrogen sulfide, synthetic and pharmaceutical applications has generated interest in their study and in the development of methods for synthesizing them selectively.[1] Sulfur-transfer reagents are useful in delivering polysulfanes with good selectivity, but the mechanism of such reactions has not been studied in detail. Herein we present our results from studies on the reactions of titanocene pentasulfide (Cp_2TiS_5) with chlorosulfanes (RSCl) as electrophiles. Additionally, a derivative of titanocene pentasulfide with an organosulfur ligand, titanocene tetrasulfide isopropylidine ($Cp_2TiS_4C(Me)_2$),[2, 3] was synthesized and its kinetic properties in reactions with chlorosulfanes were studied and compared to those of titanocene pentasulfide. Using variable temperature Stopped-Flow UV (SF-UV) and variable temperature Stopped-Flow NMR (SF-NMR) techniques we have determined the factors that govern the activation barriers of the sulfur transfer processes. Computational investigations on the reaction mechanism (KS-DFT) are in agreement with experimental results from the reactions of various titanocenes and electrophiles.



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Design and Synthesis of New Hair Clip Porphyrines for Optimization of Bistability in Solution

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Today's challenges for electronic components have changed visibly. Due to rapid progress, these are increasingly reaching their theoretical physical limits. This limit refers to both the performance and the size or miniaturization of the special components.[1,2] For several decades now, there has been a growing interest in the development of even smaller devices at the molecular level has been growing. Systems that use electron spin as the source of information storage or transmission are classified with the term "spintronics".[3,4] Based on the interconnected properties (spin-state, axial coordination and conformation) of nickel(II)porphyrins these molecules suite as building blocks for molecular spintronic devices.

In our working group this lead to the development of the hairclip porphyrin (hcp). With the incorporation of a rigid bridge with a pyridine ligand the coordination can be controlled and only two states of the porphyrin are possible (low spin, ruffled, decoordinated ↔ high spin, flat, coordinated). Scanning tunneling microscopy (STM) has proven the selective and reversible switching of individual hcp molecules on a silver(111) surface.[5]

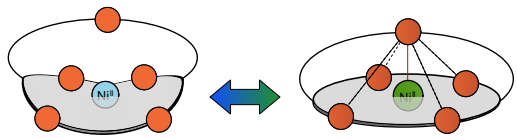

Fig. 1: Schematic illustration of the switching between uncoordinated and coordinated using different stimuli.

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Utilising Model Phosphine-Ligated Nickel Complexes to Understand sp^2-sp^2 Cross-Coupling

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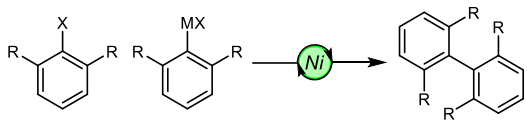
Catalysis has underpinned modern synthetic chemistry since the 1970s, driving down energetic requirements of reactions, decreasing cost and environmental impact, and opening up new synthetic targets. Its importance cannot be overstated, culminating in the 2010 Nobel Prize for Chemistry being awarded for the development of palladium-catalysed cross-coupling methods in organic synthesis. These methods often utilise platinum-group metals, with palladium-catalysed methods being the most common. These metals have a considerable environmental impact due to their low crustal abundance and the emissions resulting from their mining and processing.[1] An alternative metal for these catalytic reactions is nickel; it shares enough similarities in its properties to allow it to undertake these reactions.

Nickel has been the subject of much research into catalytic reactions, particularly in C-C and C-X bond forming reactions.[2 - 4] Our area of interest is the C-C cross-coupling of sterically hindered aryl moieties: current homogeneous nickel-catalysed methods achieve only moderate yields under forcing conditions. Our aim is to investigate the steps in the catalytic cycle, utilising model phosphine-ligated complexes to determine preferable ligand properties for some C-C cross-coupling types and understand any pitfalls within these cycles. Determination of preferred properties will enable for informed ligand use/design in future cross-couplings.



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Revisiting Rotational Isomerism of Organic Compounds

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A firm grasp of the driving forces behind conformational isomerism is crucial for the rational design of molecules with tailor-made properties. With this in mind, we reinvestigate the rotational isomerism around the C–C bond in archetypal organic compounds within the framework of Kohn-Sham molecular orbital (KS-MO) theory. Our bonding analyses reveal that overall rotational energy profiles are *always* set by steric repulsion between occupied–occupied orbitals. However, the conformational preferences can be shifted if one of the two requirements are met: i) if the relative steric repulsion is too weak and thus easily counteracted by subtle attractive interactions (*e.g.*, hyperconjugation[1]; **1** → **2**, Fig. 1); or ii) if stronger intramolecular interactions take place (*e.g.*, hydrogen bonding[2]; **1**→ **3**, Fig. 1). Our analyses lead to a novel, fundamentally revisited picture of the physical mechanisms behind well-known conformational effects in organic chemistry.

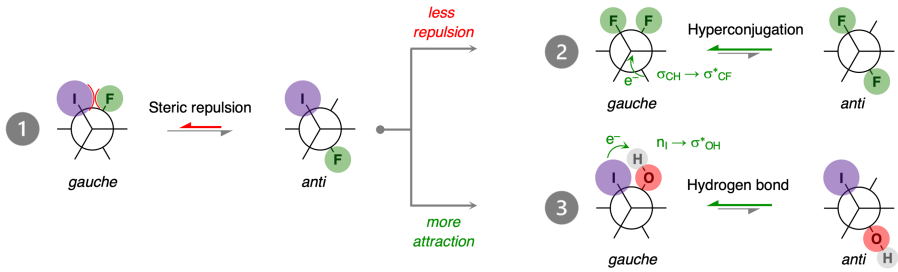

Figure 1. Conformational preferences of 1,2-disubstituted ethanes.

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ESOR2023 Amsterdam

PREDiCT: The Reaction Dynamics of the Nitrite Anion

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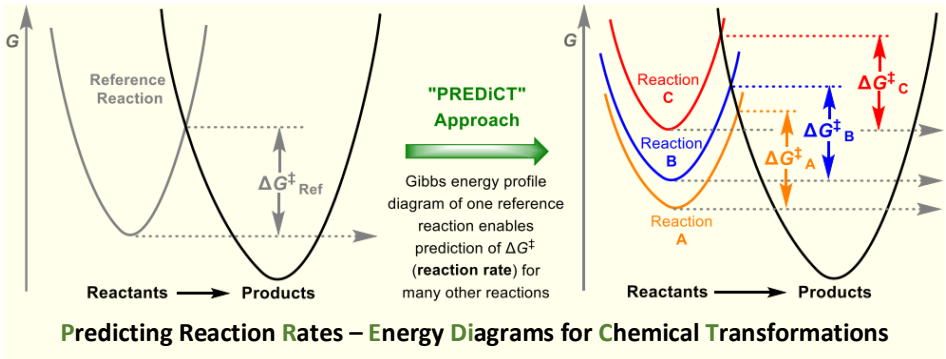

The primary aim of this project is to develop a novel method for predicting Gibbs energies of activation (the heights of activation barriers, $\Delta G^{\ddagger}$) and hence the rates of chemical reactions. The S_N2 alkylations of the nitrite anion were selected as one test case for the development of this model. A Gibbs energy profile diagram was constructed for one reference reaction by combining experimentally determined values of $\Delta G^{\ddagger}$, values of $\Delta_r G^{\circ}$ calculated at a high level of theory,[1] along with Intrinsic Reaction Coordinate (IRC) data.[3,4] For a given Series of alkylating agents (MeX, EtX) it is assumed that the Gibbs energy well of the product remains unchanged. Consequently, the values of $\Delta G^{\ddagger}$ for these related reactions can be predicted. Upon comparison with experimentally derived values, it is observed that the predictions closely reproduce activation barrier values. This work will ultimately form part of a model which aims for general predictive capability of the rates of chemical reactions. The potential impacts of such a model are far reaching and could allow for efficient synthetic planning, maximisation of yields and minimisation of contamination with impurities generated, in addition to reduction of waste generated and power consumption.

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Diaryl-hemiindigos as visible light, pH, and heat responsive four-state switches and application in photochromic transparent polymers[1]

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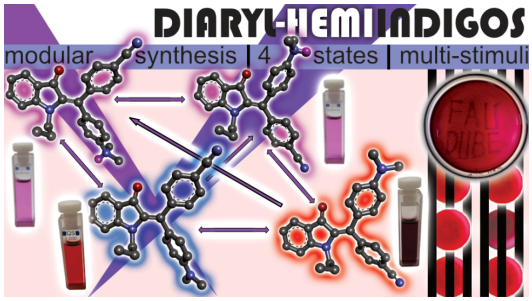

“Photoswitches are indispensable tools for responsive chemical nanosystems and are used today in almost all areas of the natural sciences. Hemiindigo (HI) derivatives have recently been introduced as potent photoswitches, but their full applicability has been hampered by the limited possibilities of their functionalization and structural modification. Here we report on a short and easy to diversify synthesis yielding diaryl-HIs bearing one additional aromatic residue at the central double bond. The resulting chromophores offer an advantageous property profile combining red-light responsiveness, high thermal bistability, strong isomer accumulations in both switching directions, strong photochromism, tunable acid responsiveness, and acid gating. With this progress, a broader structural realm becomes accessible for HI photoswitches, which can now be synthetically tailored for advanced future applications, e.g., in research on molecular machines and switches, in studies of photoisomerization mechanisms, or in the generation of smart and addressable materials. To showcase the potential of these distinct light-responsive molecular tools, we demonstrate four-state switching, chemical fueling, and reversible inscription into transparent polymers using green and red light as well as acid/base stimuli, in addition to a comprehensive photochemical study of all compounds.”[1]

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Orbital Interactions *vs* Basicity of Phosphoryl Oxygen

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The organophosphorus compounds, namely, trialkyl phosphates, phosphonate, phosphinate and phosphine oxides (Figure 1), have been extensively used for complexing actinides. The extraction ability of a particular ligand is experimentally measured in the form of distribution ratio (*D* value), which is defined as the ratio of the concentration of the metal ion in the organic to that in the aqueous phase. An increasing trend in $D_{U(VI)}$ values is observed as we move from phosphate to phosphine oxides (0.25 < 10.8 < 120 < 38) and upon elongation of the alkyl chain length in ligands (*n*-C_4H_9: 26, *n*-C_5H_{11}: 32, *n*-C_6H_{13}: 38).[1] Hitherto the assumption was that the enhanced basicity (electron density) of phosphoryl oxygen in trialkyl phosphine oxide over phosphinate, phosphonate and trialkyl phosphates, as a result of the inductive effect of attached alkyl chains, was primarily responsible for its better complexing behaviour with actinides. However, for the first time, we have demonstrated through quantum chemical calculations that it is the "dispersion and orbital interactions" and not the "phosphoryl oxygen basicity" that is primarily responsible for the better complexing ability of phosphine oxides over other molecules. The computed electronic charges (Table 1), energy decomposition and molecular orbital analysis support our argument and provide valuable insights into the selectivity of ligands for uranyl species. All calculations are carried out using ORCA version 4.2.1[2] and ADF 2016[3] program packages.

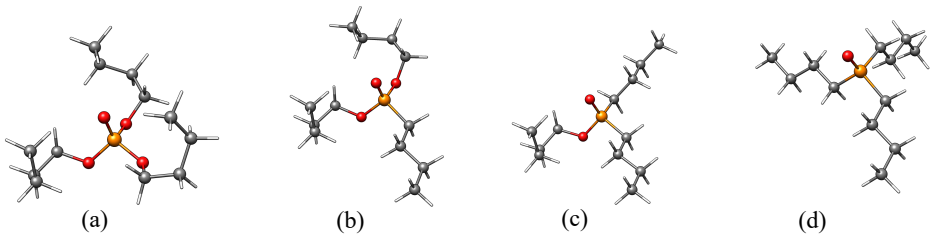

Figure 1. Lowest energy geometries of phosphate (a), phosphonate (b), phosphinate (c), and phosphine oxide (d), with butyl group as alkyl unit at RI-BP86-D3BJ/def2-TZVP level. Color code: Red is oxygen, orange is phosphorous, grey is carbon and white colour represents hydrogen.

Table 1. The calculated electronic charges for P and O in the ligands at RI-BP86-D3BJ/def2-TZVP level.

Ligands	Charges on O and P (parenthesis) atoms			*r* (P=O) in Å	*ν* (P=O) in cm^{-1}
	Mulliken	NBO	AIM		
Phosphate	–0.50 (+0.82)	–1.07 (+2.43)	–1.46 (+3.64)	1.48	1226
Phosphonate	–0.51 (+0.73)	–1.05 (+2.26)	–1.46 (+3.38)	1.49	1216
Phosphinate	–0.51 (+0.64)	–1.04 (+2.07)	–1.45 (+3.12)	1.49	1212
Phosphine oxide	–0.52 (+0.58)	–1.03 (+1.84)	–1.45 (+2.86)	1.50	1166

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Regioselectivity in the Hofmann–Löffler–Freytag Reaction: A Computational Analysis of Rearrangement Reactions

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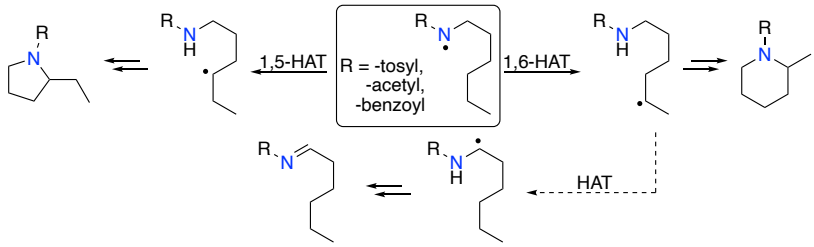
The Hofmann-Löffler-Freytag (HLF) reaction has emerged as a method for the late-stage functionalization of remote C-H bonds,[1] facilitating the synthesis of five-membered pyrrolidine rings through N-centered radicals using a 1,5-hydrogen atom transfer (HAT) process.[2] Notably, the formation of six-membered piperidine heterocycles via 1,6-HAT is prominently observed only within highly rigid or substituted systems.[3]

Our computational studies (RO-B2PLYP/G3MP2large) revealed negligible differences in both thermodynamic and kinetic parameters for the two pathways within unsubstituted alkyl chains. This finding contrasts the experimental dominance of the pyrrolidine ring formation. We delved into the impact of different nitrogen-functionalizing groups, namely tosyl, acetyl, and benzoyl, and probed into both intermolecular and intramolecular mechanisms. Further insights led us to identify other possible rearrangement reactions which likely influence regioselectivity. By harnessing these findings, we can adeptly modify HLF reaction conditions to either favor piperidine outcomes or augment overall yields. Our conclusions were corroborated by EPR and NMR studies on selected systems.



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[3] H Zhang, K Muñiz, *ACS Catal.*, **2017**, 7/6, 4122

Effect of axial solvent coordination to Rh_2-nitrene species relevant to catalytic C-H amination

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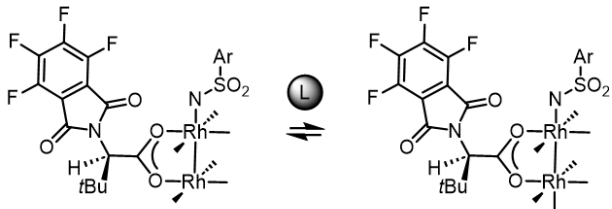

Dirhodium tetracarboxylate complexes play a prominent role in catalysis and have been intensively studied for their ability to promote the functionalization of C-C and C–H bonds. While the reactivity and selectivity of these complexes can be altered by the solvent chosen to run the reaction, the impact of its potential axial coordination has yet been unexplored. In a recent publication, the influence of axial solvent coordination to dirhodium carbenes was assessed computationally, regarding the formation of the carbene intermediate.[1] The authors indicate that the effects are small but can still influence reactivity and selectivity outcomes. In our group, the use of dirhodium chiral catalysts has made it possible to promote a variety of nitrene transfer reactions with good yields and selectivity.[2] In some cases, the choice of the solvent was found crucial.[3] In this study, we employed DFT method to assess physical, geometric and electronic changes induced in Rh-nitrene species upon solvent coordination. We also evaluated their relative reactivity towards C-H amination. Our results provide valuable insights for catalytic applications.

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From Bench-stable Carbenes to Organic Radicals

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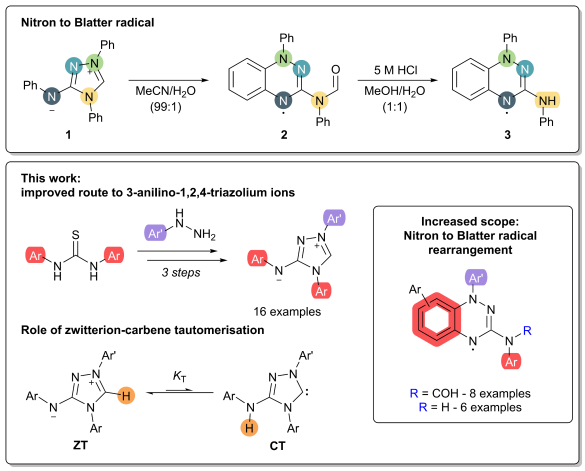
We recently reported the unusual rearrangement of a C(3)-anilino-1,2,4-triazolium ion, commonly known as Nitron **1**, into bench stable Blatter-type organic radicals **2** and **3**.[1] These benzotriazinyl radicals have seen successful application as switchable signal enhancement agents for NMR spectroscopy.[2] Only the synthesis of the parent Nitron **1** was reported prior to this work,[3] which we used to access radical derivatives with simple alkyl substituents.[1] We now report an improved synthetic route to **1**, allowing access to a broader range of C(3)-anilino-1,2,4-triazolium ions encompassing electron donating and withdrawing substituents. The range of 1,2,4-triazolium ions was evaluated in the rearrangement to Blatter radicals, with radical formation proved to be dependent on the equilibrium position (K_T) between the zwitterionic (**ZT**) and *N*-heterocyclic carbene (NHC) (**CT**) tautomeric forms of the ions. Determination of NH and C(5)-H pK_as enabled access to K_T values for zwitterion-NHC tautomerization.



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Antiaromaticity *vs* Asynchronicity

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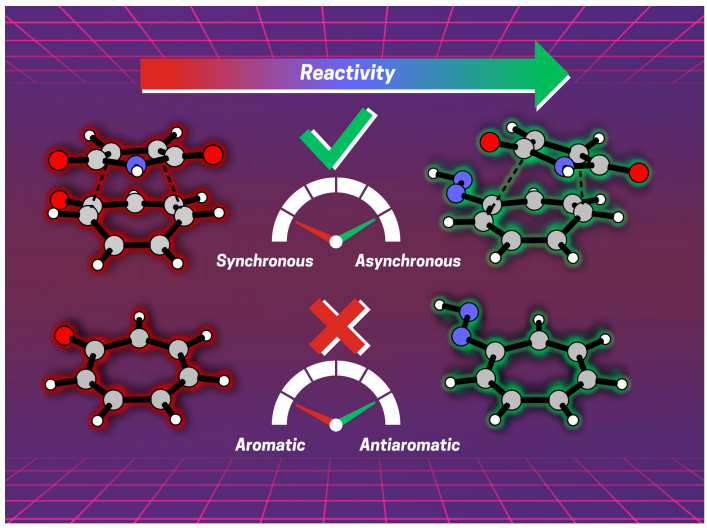
Tropone is an unreactive diene in Diels-Alder reactions, but it can be activated via carbonyl umpolung by using hydrazone ion analogs. Recently, the higher reactivity of hydrazone ion analogs was ascribed to a raised HOMO energy induced by antiaromaticity.[1] This dearomatizing HOMO-raising rationale is frequently used to explain observations in the laboratory. We, however, show that the correlation between a raised HOMO energy and a higher reactivity is not causal.[2] Instead, the real physical mechanism behind the lowering of the activation barrier is the amplified asynchronicity of the reaction mode, resulting in (i) less deformation of the reactants, and (ii) a relief in destabilizing Pauli repulsion between the deformed reactants.



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Quantitative structure–reactivity relationships for synthesis planning: The benzhydrylium case

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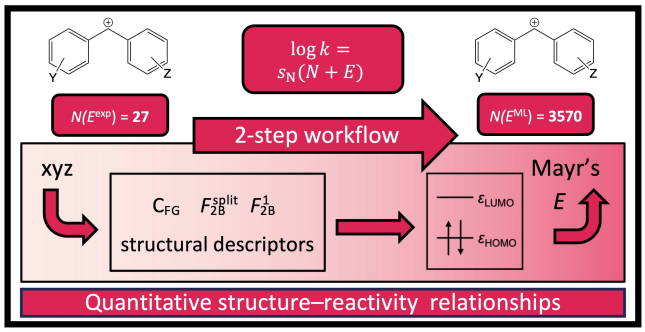
Selective and feasible reactions are top targets in synthesis planning, both of which depend on the reactivity of the molecules involved. Mayr's approach to quantifying reactivity[1] has greatly facilitated the planning process, but reactivity parameters for new compounds require time-consuming experiments. In the past decade, data-driven modeling has been gaining momentum in the field as it shows promise in terms of efficient reactivity prediction.[2] However, state-of-the-art models use quantum chemical data as input, which prevents access to real-time planning in organic synthesis.

We present a novel data-driven workflow for predicting reactivity parameters of molecules that takes only structural information as input, enabling *de facto* real-time reactivity predictions.[3] We use the well-understood chemical space of benzhydrylium ions as an example to demonstrate the functionality of the approach and the performance of the resulting quantitative structure–reactivity relationships (QSRRs). The results suggest that it is straightforward to build low-cost QSRRs that are accurate, interpretable, and transferable to yet unexplored systems within a given scope of application.



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Description of the substituent effect in polyenes, polyynes and acenes

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Our recent research focused on a detailed analysis of the substituent effect (SE) in disubstituted polyenes, polyynes and acenes (spacers) with n = 1 – 5 and 10 repeatable units (Figure 1, *left*).[1] In order to quantitatively describe the SE, homodesmotic reactions and the cSAR (*charge of the substituent active region*) parameter were used. Study also included analyses of geometry and electron delocalization with a recent EDDB (*electron density of delocalized bonds*) method. The obtained results allowed to evaluate how the SE weakens with n (Figure 1, *left*), depending on the Y group and the spacer type. The weakening is best approximated by exponential functions and differs for Y = NO_2 and O^-.

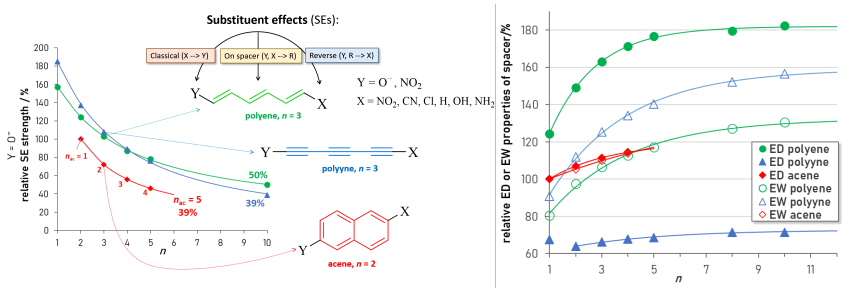

Figure 1. (*left*) Studied systems and aspects of the SEs; SE strength in % relative to the *p*-benzene derivatives as a function of spacer length, n.[1] (*right*) Electron-donating (ED) and withdrawing (EW) properties of spacers in % relative to benzene, as a function of n.[2]

For the first time, we also show how electron-donating and withdrawing properties of spacers change with n (Figure 1, *right*), and visualize the changes in electron delocalization within spacers and substituents using the EDDB method. The latter provides great insight into the nature of SEs and the interaction between substituents and spacers.

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EPR and NMR Investigation of Hofmann–Löffler–Freytag Reaction: Detection of N-centered Radical

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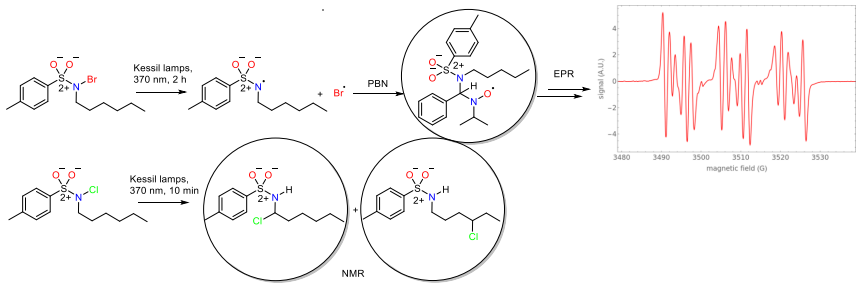
The Hofmann-Löffler-Freytag (HLF) reaction is a tool for functionalizing remote C-H bonds,[1] leading to the formation of pyrrolidine rings or C_5-substituted products. The mechanism of this reaction involves a rearrangement via 1,5-hydrogen atom transfer (HAT) from an N-centered radical. Studies by the Roizen[2] and Muñiz[3] groups have reported the formation of piperidine and C_6-halogenated products via 1,6-HAT.

We present the progress of an EPR and NMR study on *N*- and *C*-centered radical intermediates of the HLF reaction derived from N-halogen-N-alkyl-tosylamides. These radicals, produced by in situ UV light irradiation, are captured using a phenylbutylnitrone (PBN) spin trap, with the resultant adducts monitored via EPR. Our EPR measurements identified a Cl-PBN adduct produced by light in toluene experiments, substantiating that light effectively homolytically cleaves the N-Cl bond, leading to a chlorine radical that rapidly combines with PBN. Furthermore, we discerned EPR signals from spin adducts of light-induced N-centered radicals and rearrangement products, examining variations in N-halogen bonds (Cl/Br) and solvent environments (toluene/n-heptane). Conclusively, NMR data showcased the formation of several chlorinated products.



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