EuChemS Division of Organic Chemistry 14th Young Investigator Workshop (YIW2023)

Friday, 7 July 2023 – Saturday, 8 July 2023
Leuven, Belgium

Programme

Friday, 7 July 2023

Registration and coffee - MTC1 00.07 for registration, MTC1 00.03 for coffee (10:00 - 10:50)

Friday: Session 1 - Chair: Pat Guiry - MTC1 00.03 (10:50 - 13:00)

10:50	Welcome and opening	GUIRY, Pat
11:00	The Iron Age of Catalysis - A World of Opportunities	DE RUITER, Graham
11:25	Study of two protocols for the separation of heterogeneous catalysts after decarbonylation of aldehydes	AJDAČIĆ, Vladimir
11:50	Homogeneous Catalysis for Sustainable Chemistry	NIELSEN, Martin
12:15	Sponsor talk 1 - Magritek - Spinsolve benchtop NMR to speed up the organic chemistry work	BOUILLAUD, Dylan

Lunch break - MTC1 00.03 (12:40 - 14:00)

Friday: Session 2 - Chair: Ari Koskinen - MTC1 00.03 (14:00 - 16:00)

14:00	Synthesis and Applications of Planar Chiral [2.2]Paracyclophanes	BENEDETTI, Erica
14:25	Supramolecular Architectures Comprising Conformationally Flexible Cavity	JOZELIUNAITE, Augustina
14:50	Sponsor talk 2 - Boehringer Ingelheim - Discovery and synthesis of covalent HER2 selective inhibitors for the treatment of HER2 Exon 20 insertion driven tumors	WILDING, Birgit
15:10	From Liquid Crystal Dimers to Supramolecular Assemblies in Water with a Touch of Chirality	KNEŽEVIĆ, Anamarija
15:35	Oxidation of Isodiphenylfluorindine and Synthesis of Isodiphenylfluorindinone and Isodiphenylfluorindone	ZISSIMOU, Georgia

Coffee break - MTC1 00.03 (16:00 - 16:30)

Friday: Session 3 - Chair: Michael Schnürch - MTC1 00.03 (16:30 - 17:45)

16:30	Target elucidation through target degradation: Discovery of BET bromodomains as the target of Hedgehog Pathway Inhibitor 1	HOOGENDOORN, Sascha
16:55	Peptide chemical engineering: from substrate-derived inhibitors to bioconjugation techniques	TIETZE, Alesia
17:20	Peptide-Based Supramolecular Constructs	PALMA, Aniello

Dinner @ Domus Leuven (19:00 - 21:30)

Saturday, 8 July 2023

Saturday: Session 4 - Chair: Michael Schnürch - MTC1 00.03 (09:00 - 11:00)

09:00	Access to high rotational barrier atropisomers	NEOCHORITIS, Constantinos
09:25	A Modular Strategy for the Synthesis of Dothideopyrones E and F, Secondary Metabolites from an Endolichenic Fungus	SOLUM, Eirik
09:50	Sponsor talk 3 - Elsevier - The Elsevier's chemistry ecosystem	DA PIAN, Marta
10:10	Unlocking the potential of chromones and steroids to create chemical diversity and bioactive compounds	ALBUQUERQUE, Hélio
10:35	From phosphorus and sulfur – multicomponent and one pot reactions	ÁBRÁNYI-BALOGH, Péter

Coffee break - MTC1 00.03 (11:00 - 11:25)

Saturday: Session 5 - Chair: Ari Koskinen - MTC1 00.03 (11:25 - 13:25)

11:25	New Modes of Reversible Photochemistry	SLANINA, Tomáš
11:50	Factors Impacting Cage-Escape Yields in Iron(III) Photoredox Catalysis	TROIAN-GAUTIER, Ludovic
12:15	Harnessing chirality: molecules, light, properties and applications	ZINNA, Francesco
12:40	Reaction Development for the Synthesis of Conjugated Organic Materials	SCHIPPER, Derek
13:05	Sponsor talk 4 – Wiley VCH - EurJOC	TRAVAGLINI, Leana

Lunch break - MTC1 00.03 (13:25 - 14:10)

Group Picture - (14:10-14:25)

Saturday: Session 6 - Chair: Monica Oliva - MTC1 00.03 (14:25 - 16:20)

14:25	Electrochemical Deconstructive Functionalization of Cycloalkanols	MORRILL, Louis
14:50	A Radical Approach to Organic Chemistry	WEST, Julian
15:15	Sponsor talk 5 - Thieme - Synlett YIW Special Issue	BAUMANN, Stefanie
15:30	Can simple amines mimic organotin?: Aminoalkyl radicals as halogen-atom transfer (XAT) agents for redox chemistry	JULIÁ, Fabio
15:55	Towards Predictive and Operando Computational Catalysis – Recent Advancements for Transition-Metal Chemistry	PODEWITZ, Maren

Coffee break - MTC1 00.03 (16:20 - 16:45)

Saturday: Session 7 - Chair: Pat Guiry - MTC1 00.03 (16:45 - 18:00)

16:45	Synthesis of N-Heterocycles via Aryne Intermediates	ROBERTS, Courtney
17:10	All-organic Photomagnetic Switching	DUMELE, Oliver
17:35	Young Investigator Award Ceremony	GUIRY, Pat
17:45	Concluding remarks and closing	GUIRY, Pat

Dinner @ Fonduehuis Leuven (19:30 - 22:30)

THE IRON AGE OF CATALYSIS: A WORLD OF OPPORTUNITIES

Graham de Ruiter

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The continuous effort to present a more sustainable outlook for future generations has led to a renaissance in the use of earth-abundant metals in homogenous catalysis. Their natural abundance, low-toxicity, and ready availability have been strong incentives to replace their less environmentally friendly noble metal counterparts. In addition, the smaller ionic radii and typically high-spin electronic structure of earth-abundant metals have resulted in unique reactivity that can be otherwise hard to realize with their heavier congeners. Nonetheless, there are only a few examples of earth-abundant metal catalyst that can achieve noble-metal like reactivity. In this lecture, emphasis will be placed upon a new ligand design that features a central N-heterocyclic carbene (NHC) in a pincer type geometry. The resulting metal complexes of manganese, cobalt and particular iron will be evaluated for their catalytic properties. We will consider the effect of oxidation and spin-state of the observed reactivity and demonstrate that iron is indeed able to achieve noble-metal like reactivity. We will emphasize the role of two-electron chemistry in the reactivity and explore different reactions such as alkene isomerization **(Figure 1**), hydrogen isotope exchange, acceptorless dehydrogenation, and the various aspects of C−H bond activation.1-2 Overall, in this lecture it will be clear that earth-abundant metals are indeed able to break barriers in chemistry, and prepare the way for a new “iron-age” in catalysis.

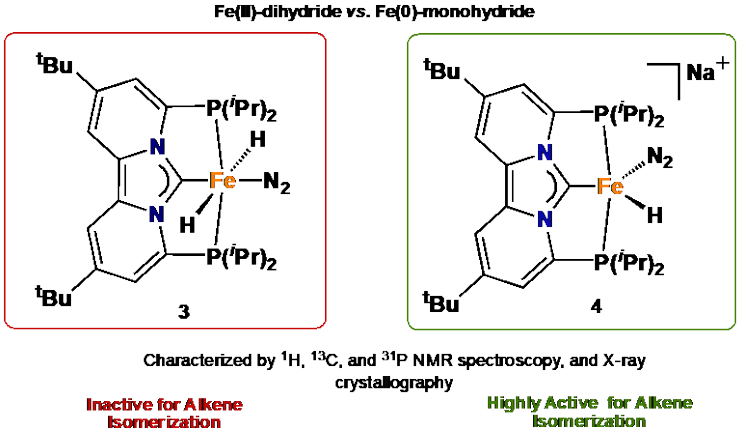

Figure 1 | Iron catalyst for alkene isomerization. Difference in oxidation and spin-state result in vast differences in reactivity for selective one-bond alkene isomerization.

References

[1] Garhwal, S.; Kaushansky, A.; Fridman, N.; Shimon, L. J. W.; and de Ruiter, G. *J. Am. Chem. Soc.* **2020**. *142*, 17131.

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Study of two protocols for the separation of heterogeneous catalysts after decarbonylation of aldehydes

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Aldehyde decarbonylation is among the most important reactions for the deoxygenation of biomaterials. Apart from industrial processes, the reaction is widely used for the synthesis of other useful molecules, including natural products [1]. Accordingly, we have described two palladium-catalyzed aldehyde decarbonylation reactions and two efficient methods for separating the expensive palladium catalyst from the reaction mixture (Figure 1).

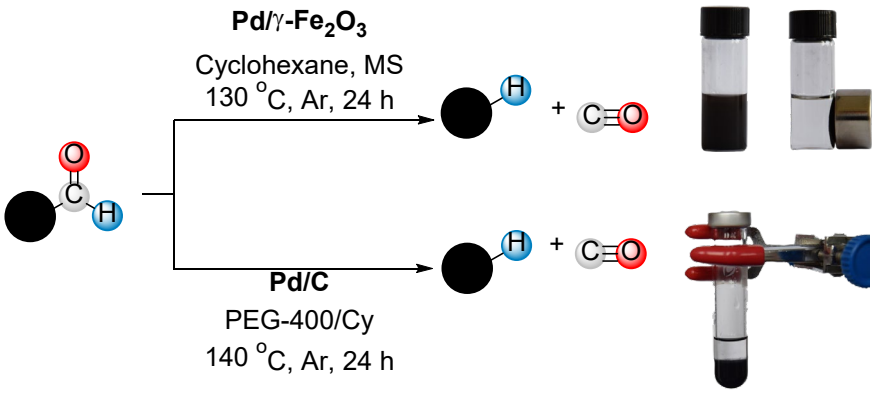

Figure 1.

The first method entails palladium immobilization on γ-Fe_2O_3, which endows the catalyst with magnetic properties and allows its efficient recovery and reusability [2]. The second separation method is based on the differential distribution of commercially available Pd/C and organic products in a mixture of PEG-400 and cyclohexane [3].

References

[1] Ž. Selaković, A. M. Nikolić, V. Ajdačić and I. M. Opsenica, *Eur. J. Org. Chem.*, **2022**, *e202101265*.
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[3] N. Terzić-Jovanović and V. Ajdačić, *J. Serb. Chem. Soc.*, **2022**, *87*, 669.

Homogeneous Catalysis for Sustainable Chemistry

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To reach an environmentally sustainable society, fundamental new developments must be made within the vast field of chemistry. For example, CO_2 utilization, e.g. for use as building block in the chemical industry rather than simple CO_2 storage, can significantly contribute to CO_2 abatement, biomass upgrade to commodity chemicals can lead to a carbon negative footprint, and liquid chemical H_2 storage can revolutionize the energy- and fuel- grids. However, despite these colossal potential benefits, the developments of all three sustainable transformations are in their infancy and are yet to become viable industrial processes.

The use of homogeneous catalysis has long been recognized as the superior choice with respect to reaction selectivity and efficacy. Nevertheless, it remains to be seen that this type of catalysis can mediate any of the above-mentioned transformations under sustainable conditions while maintaining a high efficacy and long catalytic-system longevity.

The Nielsen lab has repeatedly shown how biogenic compounds such as ethanol, levulinic acids, furanics, mono- and polysaccharides, and even raw biomass all are converted to industrially value-added compounds such as primary- and secondary alcohols, hydrocarbons, furfuryl alcohols, and γ-valerolactone (GVL) using organometallic catalysis under mild condition and with best-in-class catalyst performances.

In my talk, I will show how several of these reports not only represent state-of-the-art reactivity profiles, but also disclose novel catalytic behaviour. For example, we demonstrate the first example of ethanol upgrading to secondary alcohols [1], which will open for the usage of bioethanol as platform compound to a much larger library of target molecules than we see today.

We furthermore show that Noyori-type pincer catalysts can be rendered catalytically active for hydrogenation in the presence of an acid, even though this catalyst type has long been recognized to require either neutral or basic conditions to stay functional. I will demonstrate its high usefulness by showing that this unique combination of acid and a hydrogenation catalyst allows for unprecedented valorisation of numerous biomass waste sources to GVL [2].

I will also show how a novel combination of an organometallic catalyst and ionic liquid provides energy-efficient reversible CO_2 hydrogenation to formic acid [3]. Such a system is a potential powerful tool for H_2 storage, e.g. in H_2 batteries, and in hydrogen-based transportation.

Finally, I will share recent findings on how a novel in-house developed organometallic complex salt shows different chemoselectivities for catalytic transfer hydrogenation of aldehydes, ketones, alkenes, and alkynes depending on the choice of the seemingly innocent counter anion to the complex cation [4].

References

[1] Z. Ni, R. Padilla, L. D. S. Mello and M. Nielsen, *ACS Catalysis*, **2023**, *13*, 5449.
[2] S. Koranchalil and M. Nielsen, **2023**, *Submitted*.
[3] L. Piccirilli, B. Rabell, R. Padilla, A. Riisager, S. Das and M. Nielsen, *J. Am. Chem. Soc.*, **2023**, *145*, 5655.
[4] D. L. J. Pinheiro, J. T. M. Correia, M. S. B. Jørgensen and M. Nielsen, *Manuscript under preparation*.

Spinsolve benchtop NMR to speed up the organic chemistry work

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The need of NMR spectroscopy data for organic chemists is obvious for structural elucidation and reaction control purposes. Spinsolve brings NMR spectroscopy directly in the laboratory, next to the reactor. It allows the users to skip many time-consuming sample preparation steps and have structural information on raw mixture within a few minutes. This presentation explains the latest development allowing the users to perform powerful 1D, 2D, diffusion, multinuclear NMR analyses on your daily reactions.

Founded in 2004, Magritek is the global leader in manufacturing cryogen-free benchtop Nuclear Magnetic Resonance (NMR) spectrometers for the analytical instrument market. Magritek's revolutionary 90 MHz, 80 MHz and 60 MHz Spinsolve family of benchtop NMR models offer the highest sensitivity and resolution available in the market. These portable systems are robust and easy to use, allowing modern NMR methods to be performed on the chemistry lab bench or inside the fume hood next to a reactor.

Synthesis and Applications of Planar Chiral [2.2]Paracyclophanes

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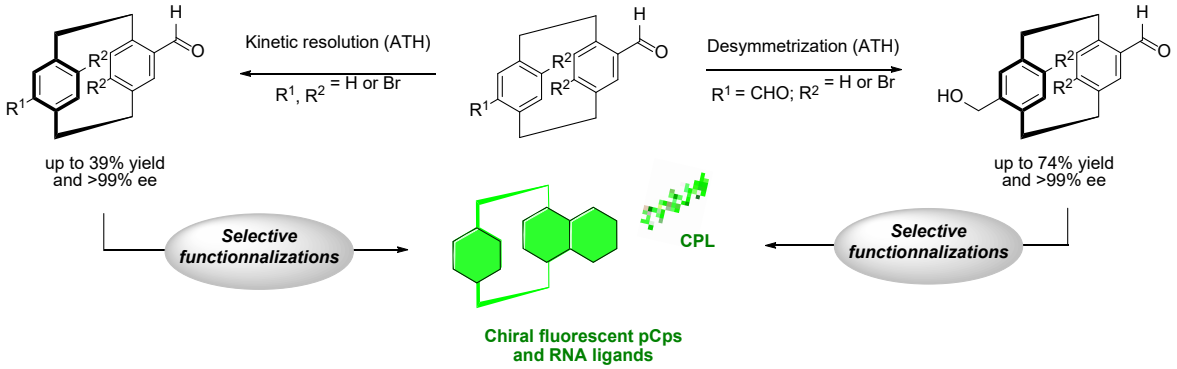
Originally discovered in a serendipitous fashion by vapor phase pyrolysis of *p*-xylene [1], [2.2]paracyclophanes (pCps) have rapidly gained popularity amongst chemists due to their unique three-dimensional architecture [2] that can give rise to planar chirality [3]. Despite their advantageous physicochemical properties and potentially wide range of applications, optically active pCps are still mainly obtained through enantiomer separation by chromatography on chiral stationary phases. The optimization of new asymmetric processes providing a practical access to enantiopure pCps can therefore be considered as a priority in modern cyclophane chemistry.

Our group has developed a general approach based on asymmetric transfer hydrogenations (ATH) for controlling the planar chirality of a range of substituted pCps. This strategy enables us to perform both the kinetic resolution of racemic compounds [4] and the desymmetrization of centrosymmetric *meso* derivatives [5] on synthetically useful scales. The obtained enantioenriched molecules, which incorporate different reactive groups on each ring of the pCp core, can be used as key intermediates for the preparation of new circularly polarized light (CPL) emitting dyes [6-7] and RNA ligands [8]. Based on its broad applicability, our method should constitute an extremely useful tool to rapidly access complex pCps in their enantiopure form. This convenient approach may reveal useful to further expand the range of applications of these original planar chiral objects in different research fields.



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[4] M.-L. Delcourt, S. Turcaud, E. Benedetti and L. Micouin, *Adv. Synth. Catal.*, **2016**, *358*, 1213.
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Supramolecular Architectures Comprising Conformationally Flexible Cavity

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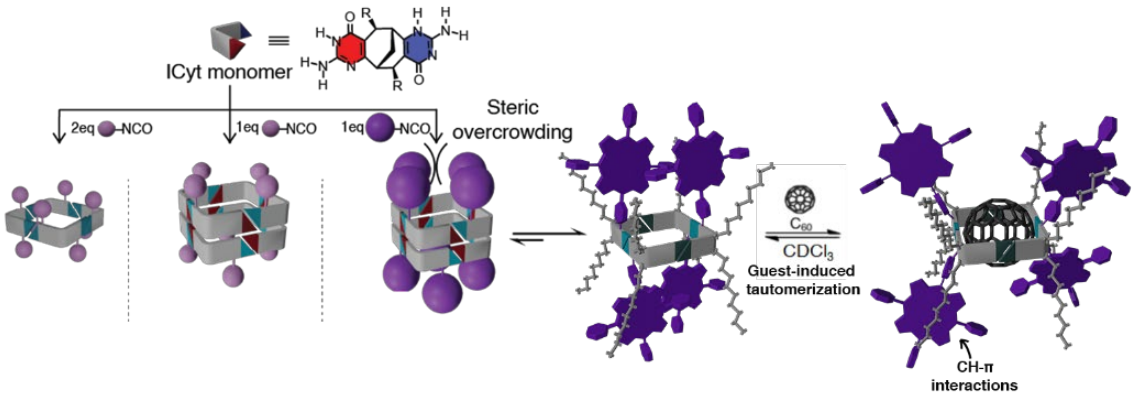
Supramolecular chemistry has grown tremendously by implementing insights acquired from biological processes into state-of-art architectures at the molecular level. The next stage is to introduce function into the supramolecular architectures, however, synthetic self-assembling systems are still underdeveloped, and there are several challenges that must be overcome before fully functional molecular devices can be achieved. The individual components utilized in the bottom-up construction must be equipped with appropriate shape and symmetry to be able to aggregate in well-defined, controlled manner and to overcome the entropic penalty arising from the loss of disorder. The current discoveries in the field emphasize on more dynamic models of molecular recognition, such as induced-fit and conformational selection in pursuit of synthetic receptors, catalysts or cross-membrane transporters. These advances stress the necessity to go beyond conventional rigid supramolecular architectures, challenging us to develop reversible biomimetic supramolecular systems encompassing conformationally flexible frameworks.

To contribute to these efforts, we became interested in development of hollow supramolecular architectures with adaptable cavity utilizing enantiopure bicyclo[3.3.1]nonane monomers. The cavity size of the supramolecular capsules was tuned by introducing different types of hydrogen-bonding modes into the system. Asymmetrical bicyclo[3.3.1]nonane monomers embedded with isocytosine and ureidopyrimidinone units on opposite sides tends to assemble into octameric tubes as a result of social self-sorting. We anticipated that introduction of bulky tetraphenylporphyrin urea substituents could be used as a straightforward approach to access different binding properties, without the necessity to redesign the whole hydrogen-bonding motif. Additionally, the dynamic nature of concave capsule was demonstrated by entrapping fullerene C_{60} as a guest. Remarkably, guest molecule induced the conformational changes of the host needed for efficient accommodation of the guest by shifting the equilibrium from closed to open-ended form [1].



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Discovery and synthesis of covalent HER2 selective inhibitors for the treatment of HER2 Exon 20 insertion driven tumors

Birgit Wilding, Ralph Neumueller, Flavio Solca, Dirk Scharn, Dietrich Böse, Anke Baum, Stefan Kornigg, Petr Knesl, Guido Scholz, Jens Bruchhaus, Markus Spina, Josef Balla, Biljana Peric-Simov, Jasmin Zimmer, Sophie Mitzner, Thomas N. Fett, Gerd Bader, Matthias Treu, Julian E. Fuchs, Stephan Zahn, Peter Ettmayer, Mark Pearson, Mark Petronczki, Norbert Kraut, Darryl B. McConnell

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Oncogenic mutations in human epidermal growth factor receptor 2 (HER2) occur in 2-3% of patients with non-small cell lung cancer. Many known inhibitors of HER2 are limited by adverse events resulting from inhibition of EGFR wild type. We therefore initiated a drug discovery program aiming at finding novel HER2 selective inhibitors sparing EGFR wild type activity.
Here, we report the synthesis, medicinal chemistry optimization, and pharmacological characterization of novel selective HER2 exon 20 mutation inhibitors. The presentation will focus on structure-based design efforts which resulted in new, orally bioavailable inhibitors that show excellent potency on HER2, including hard-to-hit mutations. The synthetic routes for the preparation of these novel inhibitors will also be discussed.

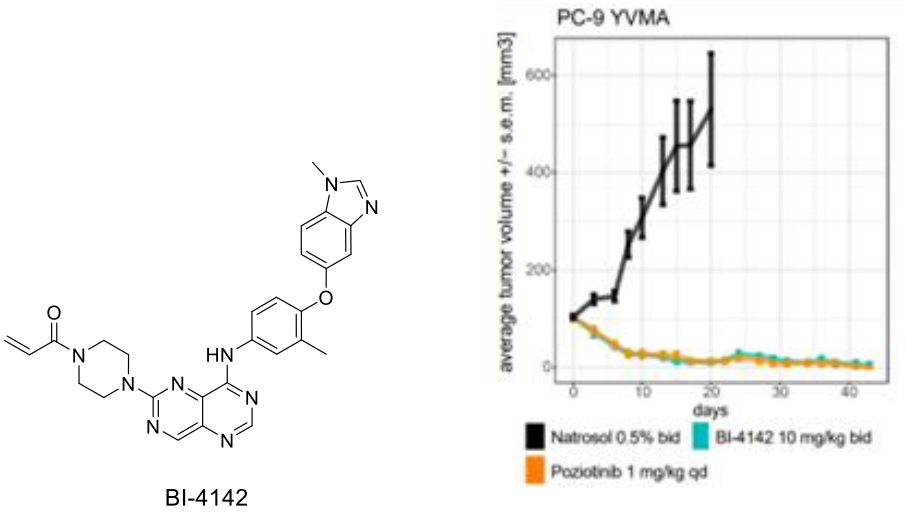

Figure 1. left panel, chemical structure of BI-4142,
right panel, xenotransplantation experiment using PC-9 HER2^{YVMA} cells with compounds and doses indicated. Natrosol, n = 10 animals; BI-4142, n = 8 animals; and poziotinib, n = 8 animals.

Upon treatment with the inhibitors, cancer cell survival and proliferation were reduced, which translated into tumor regressions in preclinical xenotransplantation models of HER2 exon 20 mutant driven cancers [1]. Our results suggest that HER2 exon 20 insertions can be effectively treated by a potent and highly selective HER2 inhibitor that spares EGFR wild type. These findings show the successful optimization of a covalent inhibitor and warrant clinical testing of covalent HER2 selective, EGFR wild type sparing inhibitors in HER2 mutant NSCLC patients.

References

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From Liquid Crystal Dimers to Supramolecular Assemblies in Water with a Touch of Chirality

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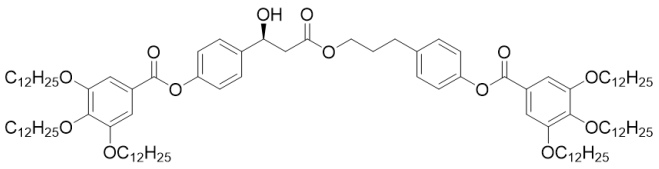
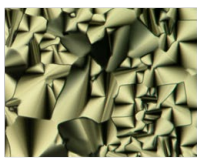
Over the past few decades, there has been a focus on self-assembly and supramolecular chemistry for the development of new organic materials, such as monolayers, nanostructures, gels, membranes, and liquid crystals [1]. The properties of these functional supramolecular materials depend both on the molecular structure of the building blocks and the conditions under which the materials are assembled [2].

The self-assembly process of mesogenic molecules is driven by the same intermolecular interactions regardless of whether it occurs in solution or in bulk. However, studies that compare these closely related systems are scarce [3]. The self-assembly of mesogenic molecules in bulk, which is temperature-dependent, results in formation of liquid crystal (LC) phases with a wide range of properties. In a similar vein, molecular building blocks in liquid media generate nanomaterials with diverse features interesting for technological and biomedical applications, particularly when the liquid is water.

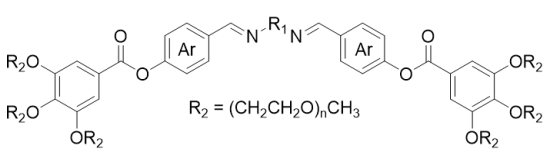
Herein, the structure-property relationship of LC flexible dimers will be discussed, with an emphasis on chiral LCs [4], a distinct class of LCs with unique optical and mechanical properties. Here, the chiral 3-aryl-3-hydroxypropanoic ester moiety has demonstrated its versatility as a building block for the preparation of chiral LC compounds. Furthermore, the transformation of LC molecules into amphiphilic molecules, shaped by the design of LC dimers, will be elucidated. The replacement of alkyl chains in the structure of LC dimers with oligo(ethylene glycol) chains provides water-soluble molecules that self-assemble into supramolecular structures forming hydrophobic pockets. The development of these water-soluble molecules holds significant potential in the creation of novel materials.



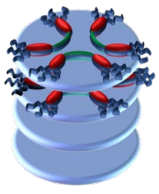
LC dimer



Columnar LC phase



Amphiphilic dimer



Nanotubes in water

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Oxidation of Isodiphenylfluorindine and Synthesis of Isodiphenylfluorindinone and Isodiphenylfluorindone

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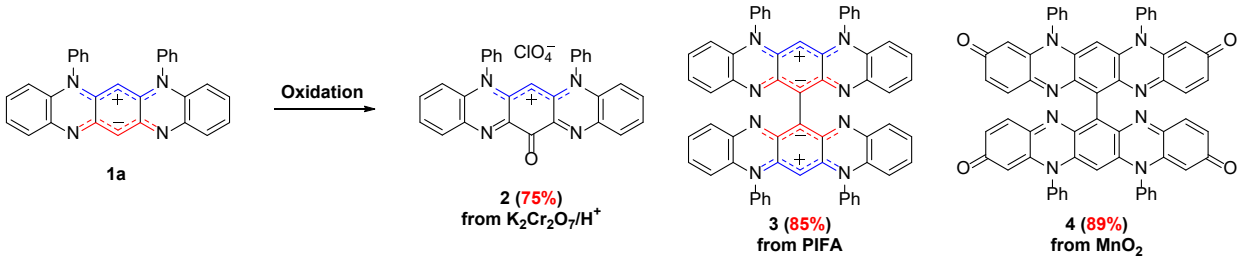
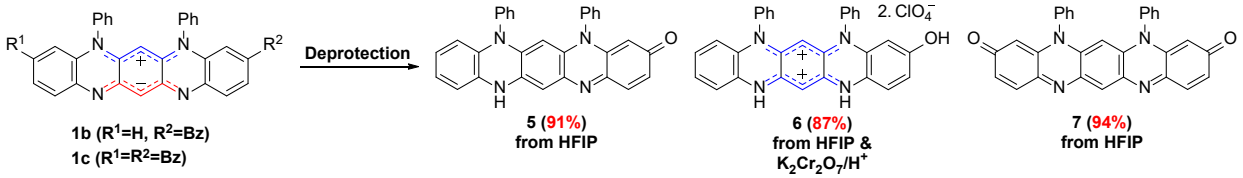
Isodiphenylfluorindine **1a** [1] and its quaternary salts are known dyes (fiber, textile, keratin) and inks (printers, ink balls, etc.), while recently, **1a** and its analogues, attracted interest as electroactive components and optical chromophores. Herein, we present its oxidative stability.

Oxidation of isodiphenylfluorindine **1a** with $K_2Cr_2O_7/H^+$ gives 13-oxo-isodiphenylfluorindinium perchlorate **2** (75%), while the zwitterionic and quinoidal cruciform 13,13'-dimers **3** (85%) and **4** (89%), are obtained from PIFA and MnO_2 oxidants, respectively [2]. The zwitterionic 13,13'-dimer **3** can be rapidly converted to the quinoidal 13,13'-dimer **4** (100%), with MnO_2 [2].



The C3- and C3,C9-oxo analogues of isodiphenylfluorindine **1a**, *i.e.* isodiphenylfluorindinone **5** and isodiphenylfluorindone **7**, which were postulated a century ago [3], cannot be obtained by direct oxidation of **1a**. An alternative path was followed, where deprotection of the C3- and C3,C9-benzoyloxy isodiphenylfluorindines **1b** and **1c** in HFIP gave isodiphenylfluorindinone **5** and isodiphenylfluorindone **7**, respectively [3]. Isodiphenylfluorindinone bisperchlorate **6** was also synthesized [3]. Optical and electrochemical behavior, along with selected theoretical studies are also presented.



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Target elucidation through target degradation: discovery of BET bromodomains as the target of Hedgehog Pathway Inhibitor-1

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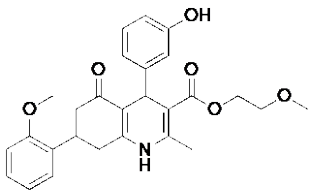
Phenotypic screens are powerful to identify small molecules that act on a biological process of interest, but the elucidation of the cellular target and/or mechanism of action of the hit compounds presents a major challenge. Consequently, hit compounds often do not reach their full potential as pharmacological leads or chemical biology tool compounds.

Exemplary of this, Hedgehog Pathway Inhibitor 1 (HPI-1) was found as a hit in a phenotypic screen for the Hedgehog (Hh) signaling pathway – a major developmental signaling cascade that establishes the embryonic body plan, and dysregulation of which underlies various cancers [1]. HPI-1 robustly inhibits the Hh pathway in a variety of cell lines, downstream of the activator Smoothened, yet its cellular target has remained elusive for many years.



HPI-1

Here, we present the target elucidation of HPI-1 through the design, synthesis, and evaluation of corresponding proteolysis targeting chimeras (Hedgehog Pathway PROTACs, HPPs) coupled with label-free quantitative proteomics [2]. We show that HPP-9 robustly reports on HPI-1 action on various BET bromodomain proteins, epigenetic modulators known to be important for Hedgehog signal transduction, through their degradation. Moreover, HPP-9 is the first example of a PROTAC targeting the Hedgehog pathway, enabling novel pharmacological strategies to combat Hh pathway-driven disease.

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Peptide chemical engineering: from substrate-derived inhibitors to bioconjugation techniques

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Peptide chemical engineering gained substantial relevance in the field of diagnostics and therapeutics. The rapid development of drug-resistant bacteria is a serious healthcare threat that prompted the exploration of new antibacterial targets. Targeting bacterial virulence, instead of developing bactericidal compounds, became a promising strategy to block pathogenicity by disarming pathogens without affecting bacterial viability. Resulting in less selective pressure on the development of antibiotic resistance. Recently, we have reached a milestone in targeting an essential virulence factor of Gram-positive pathogenic bacteria, i.e. *S. aureus* Sortase A (SrtA), which has remained an unmet challenge for many years. In our studies we have developed the first non-covalent peptidomimetic inhibitors of SrtA, already showing promising *in vitro* activity towards growth and biofilm inhibition in pathogenic *S. aureus*. Our results outline the strategy to successfully turn a peptide substrate into an inhibitor, which is of great importance and interest in the strongly emerging field of new modalities and drug discovery. Combined with our computational studies, we have established a pharmacophore model, allowing us to pinpoint the important interactions for activity.

Another important emerging field is the development of site-specific conjugation approaches, notably for the synthesis of biochemical probes or molecular conjugates for targeted delivery. We report a mild ionic liquid (IL)-mediated thiolation technique that relies on the use of IL as a solvent and precursor to generate activated IL, as well as a solvent for the conjugation reaction. First, a focused library of active ILs was prepared for functionalizing/conjugating cysteine-containing small molecules and unprotected peptides. Interestingly, a bifunctional active IL could also be successfully employed as a linker for the conjugation of peptides lacking Cys. This study sets the ground for further investigation of the use of active ILs for modifying, labeling, or conjugating of larger and more complex therapeutic modalities such as proteins and antibodies.

Peptide-Based Supramolecular Constructs

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The rational design of supramolecular constructs using bio-inspired building blocks is an ever-growing research field. In this talk, I will introduce a class of peptides, polyproline helices, that can be used as supramolecular building blocks to rationally design supramolecular responsive frameworks as well as discrete supramolecular nano-constructs.

Polyproline helices are secondary structures which appear in most proteins. They have a similar occurrence in nature to 3(10) and α helices. These helices present a high proportion of proline amino acids in their primary structure. This type of biopolymer can interconvert between two different secondary conformations as a function of the environment it is exposed to *i.e.* temperature, solvent polarity and pH (Figure 1a, polyproline II, left-handed helix with all trans conformations of the amide bonds and polyproline I, right-handed helix with all cis conformations of the amide bonds). Moreover, polyproline helices, have been shown to be extraordinarily tolerant to different functionalities [1,2].

We have recently demonstrated how this class of peptides, can self-assemble into a peptide framework capable of thermal activation, guest-induced dynamic porosity and enantioselective guest inclusion [3]. Based on these results, we were able to show how oligoproline tetramers can be specifically designed and functionalised, allowing predictable tuning of supramolecular interactions, to engineer the formation of supramolecular peptide frameworks with varying properties [4] (Figure 1b).

Finally, applying the knowledge acquired about these peptides, I will demonstrate how polyproline resilience to functionalities and periodicity, can be used to translate the design principles developed for classical metallo-organic systems to peptide-based ligands, in order to rationally synthesise the first examples of chiral, metallo-peptide cavities (Figure 1c).

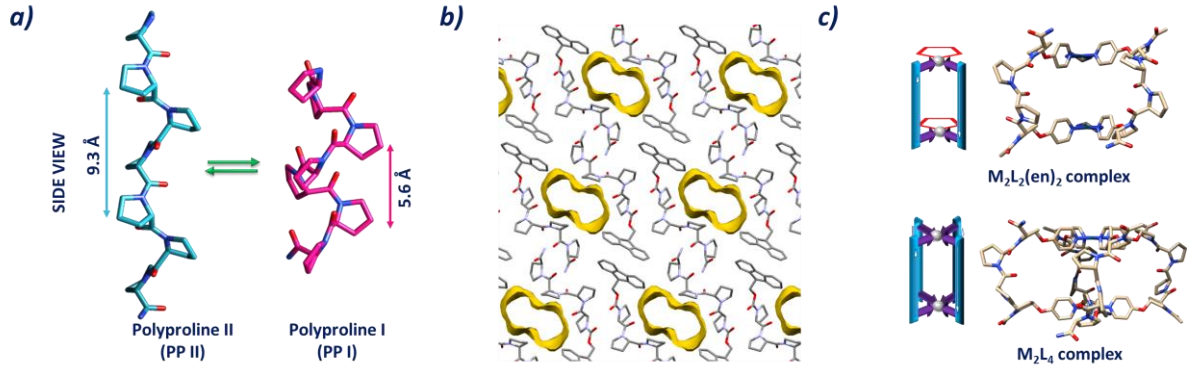

Figure 1 a) Polyproline helices I & II; b) Crystal structure of **PP_4(-SPF)**, 50 % ellipsoids (Mercury), view along the *b* axis; c) Polyproline functionalised with two monodentate pyridine coordinating functional groups *CFG* to form two metallo-peptide complexes (homoleptic and heteroleptic).

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Access to high rotational barrier atropisomers

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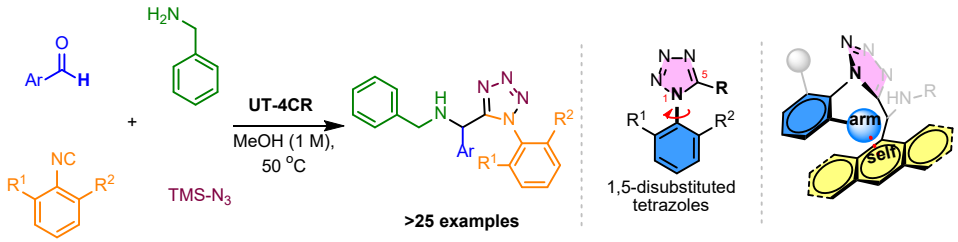
Abstract

The today's drug discovery is profoundly affected by chirality; enantiomers may differ significantly in biological activity with tremendous impact. Atropisomerism is a type of axial chirality resulting from hindered rotation of a σ bond that yields non superimposable stereoisomers (coined as "atropisomers"). The phenonemenon has been widely applied in materials, asymmetric organic synthesis and of course pharmaceuticals. Most of the atropisomers have low energy barriers (*class 1, ΔE_{rot} < 20 kcal/mol*), thus rapidly equilibrating. Nowadays, in drug discovery, it is almost prohibited to synthesize class 2 atropisomers (ΔE_{rot} ≈ *20-30 kcal/mol*), whereas it is highly recommended that molecules with one or more atropisomeric axes has to be developed as class 3 *(>30 kcal/mol*). However, the synthetic access to such molecules might be extremely challenging [1,2].

Herein, we would like to report for the first time, a synthetic access to high rotational barrier atropisomers via multicomponent reaction chemistry (MCRs). A novel class of atropisomers is reported through a Ugi-tetrazole multicomponent reaction (UT-4CR) using various aromatic and polyaromatic aldehydes, benzylamine, ortho-substituted phenyl isocyanides and trimethyl silyl azide to afford the corresponding products in high yields (Scheme 1). Several single crystal structures have been obtained demonstrating the effect, combined with DFT calculations and NMR studies.

The research project was supported by the Hellenic Foundation for Research and Innovation (H.F.R.I.) under the "2nd Call for H.F.R.I. Research Projects to support Post-Doctoral Researchers" (Project Number: 0911).



Scheme 1. Access to atropisomers via MCRs; the development of hetero biaryl atropisomers based on the UT-4CR

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A Modular Strategy for the Synthesis of Dothideopyrones E and F, Secondary Metabolites from an Endolichenic Fungus

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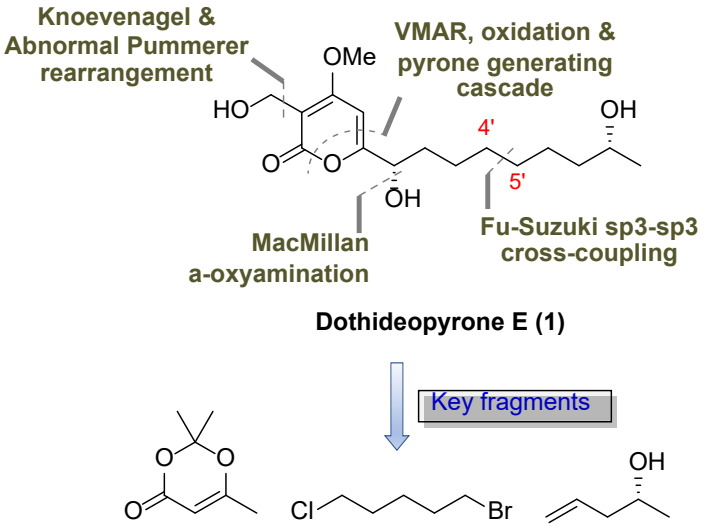
Endolichenic fungi are a rich source of natural products with a wide range of potent bioactions [1]. Dothideopyrone E (**1**) was isolated in 2018 from a culture of the endolichenic fungus Dothideomycetes sp. EL003334 [2].

Said natural product has been highlighted as a promising therapeutic lead-agent to prevent neurodegenerative diseases [2]. Given our interest in naturally occurring compounds, especially related to anti-inflammatory properties, this attracted our attention. Our progress towards realizing an efficient synthesis of dothideopyrone E (**1**) will be presented [3].



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Unlocking the potential of chromones and steroids to create chemical diversity and bioactive compounds

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Chromones and steroids are very well-known scaffolds for many different reasons. In the case of chromones, they are acknowledged not only for their wide range of biological activities, but also for their utility in synthetic chemistry as building blocks for a plethora of new compounds. Among steroids, cholesterol is perhaps the most recognizable element, playing a crucial role in the structural components of cell membranes, being also a precursor of steroid hormones and vitamin D. Its synthetic utility is not so foreseeable as for chromones, but it possible to take advantage of its hydroxy group to install heterocyclic moieties. Furthermore, the amphiphilic nature of cholesterol can be important to block certain undesirable biological processes such as misfolded protein aggregation.

Herein, chromones **1** and cholesterol **2** were used as synthons and building blocks to unlock a diverse range of new structures, some of them displaying interesting biological activities (Figure 1). Pyrrolidines **3**, pyrazoles **4**, chromeno[3,4-*b*]xanthones **5** and nitrobenzenes **6** were synthesized from chromones tethered with appropriate functionalities, through simple synthetic methods [1-3]. Noteworthy, the chromeno[3,4-*b*]xanthones **5** were further disclosed as new AChE and Aβ aggregation inhibitors [4]. In turn, cholesterol **2** was used as amphiphilic building block to produce steroid–quinoline hybrids **8**, with remarkable capacity against protein aggregation processes [5], as well as the 4*H*-pyrane tethered steroid **7**.

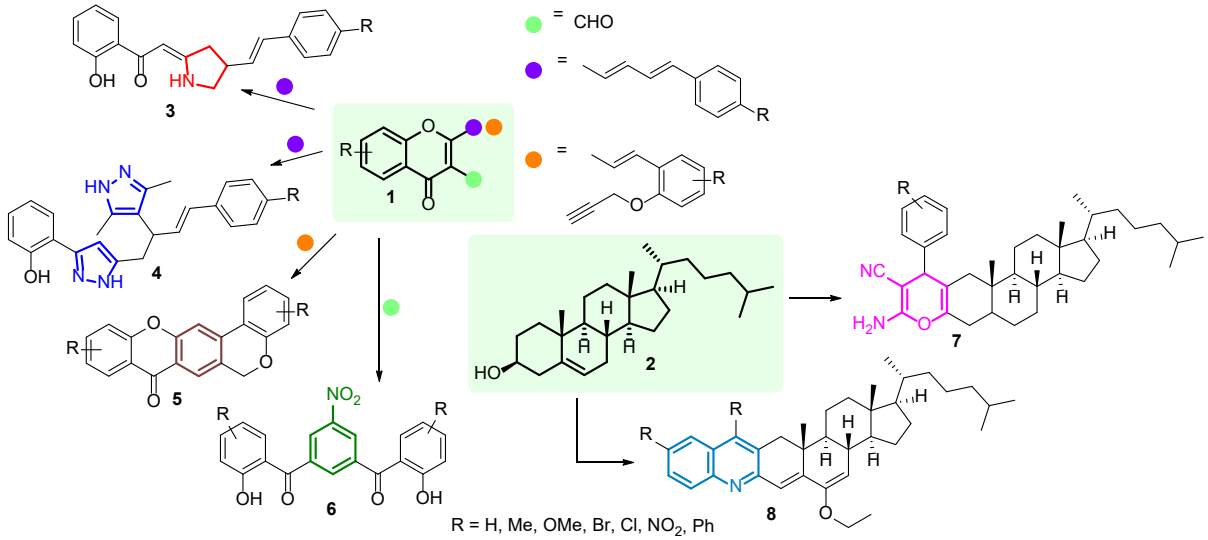

Figure 1. Chromones and cholesterol as versatile synthons unlocking new bioactive molecules.

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From phosphorus and sulfur – multicomponent and one pot reactions

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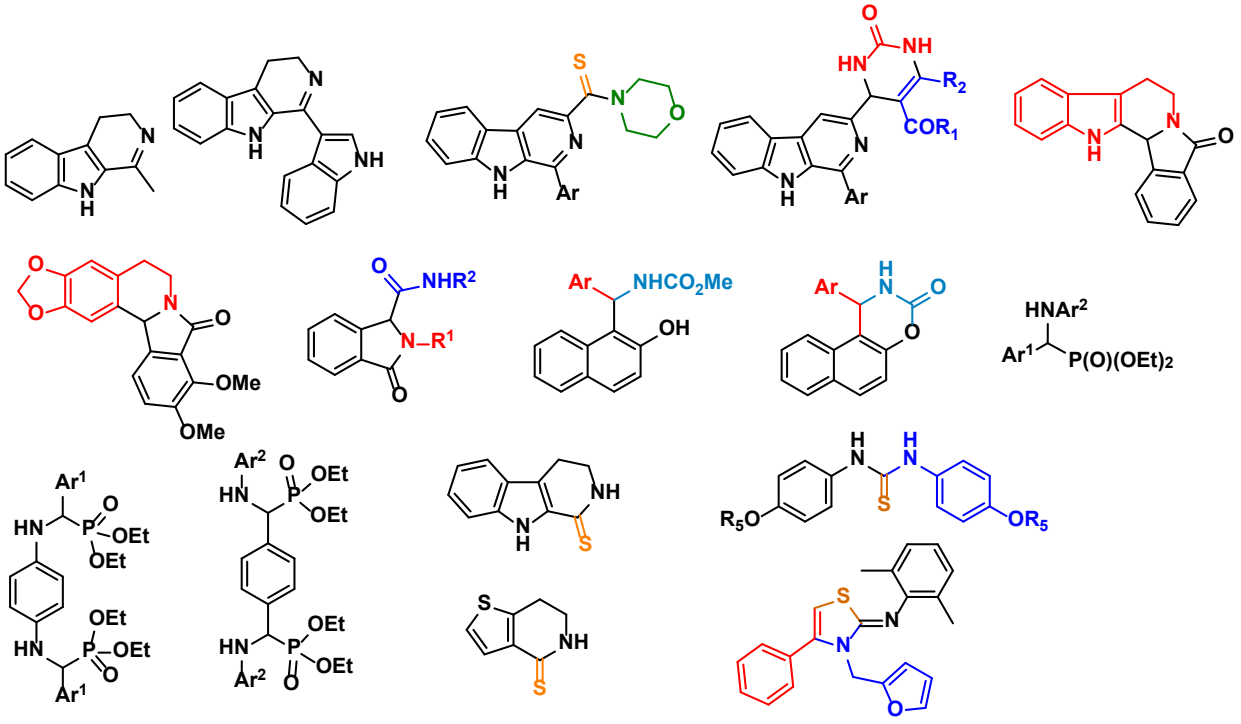
Investigating the main trends in organic and medicinal chemistry, recent studies presented that only a small number of organic molecules from the whole chemistry space with poor variety have already been prepared and a limited number reactions dominate among synthetic applications. Therefore, it is highly encouraged to develop innovative chemistries, and moreover, in order to expand the boundaries in reaction parameters, new technologies are also emerging. Besides, the “green” applications in organic synthesis (atomic efficiency, one-pot procedures, selective reactions) are getting important in laboratory and also in industrial practice.

The main goal of our research was the development of new synthetic pathways to potentially biologically active compounds and new heterocyclic cores through multicomponent/one – pot/cascade reactions. We show the applications of Bischler-Napieralski, Pictet-Spengler, Biginelli, Willgerodt-Kindler, Kabachnik-Fields and Betti reactions. We have discovered new applications of the efficient reagent T3P®, developed multicomponent aqueous reactions using elemental sulfur as the sulfurating agent and used microwave and flow chemistry to improve the synthetic efficiency. During these studies we have developed new synthetic pathways to nuevamine, harmalan and eudistomin alkaloids in addition to thiocarlide a drug used against tuberculosis.



New Modes of Reversible Photochemistry

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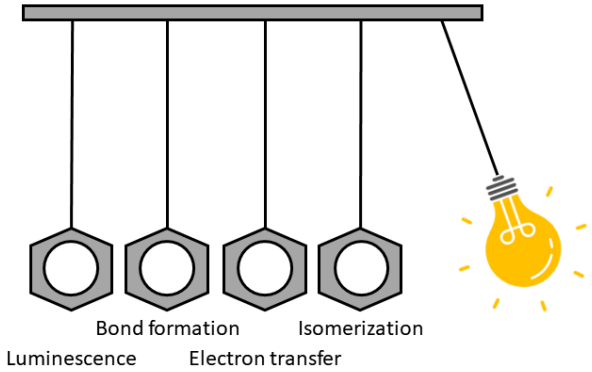
The classical approach for achieving photochemical reversibility is the use of photoswitches. These molecules can be interconverted between two forms by the light of different wavelengths. Formally, two forms of a photoswitch are the products of photoisomerization (e.g., electrocyclization or isomerization). While this strategy has been utilized in many applications, such as smart materials [1], photopharmacology [2] and molecular electronics [3], we believe that many other modes of photoinduced reversible systems are possible (see figure below).



We combine redox and photochemical processes to selectively manipulate photoswitches and develop novel systems capable of reversible transformation upon irradiation. We focus on (i) programmable gated photoswitches, such as fulgides [4] and diarylethenes, (ii) photoinduced manipulation with electrons ("electron ping-pong") and (iii) reversible formation and cleavage of covalent bonds between two molecules ("catch-and-release" strategy) [5-6]. We also reversibly modulate the luminescence of molecular systems by the light of a specific wavelength.

While these approaches diversify in terms of potential applications, the fundamental design principles are analogic to the development of photoswitches, namely optimization of wavelength orthogonality, quantum yields, dark stability and photostationary state composition. Combined, these next-generation reversible photochemical systems broaden the scope of photoactivatable molecules [7] applied in chemical biology, molecular electronics, photovoltaics, and material chemistry.

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Factors Impacting Cage-Escape Yields in Iron(III) Photoredox Catalysis

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In natural and artificial photosynthesis, light absorption and catalysis are separate processes linked together by exergonic electron transfer. There is a plethora of organic transformations that can be sensitized to visible light, but the corresponding reaction mechanisms are not always straightforward. Here, we will present recent advances in the field of mechanistic photoredox catalysis by means of steady-state and time-resolved spectroscopies. A special emphasis will be placed on cage-escape yields, i.e. the efficiency with which the radicals formed after excited-state electron transfer separate and escape the solvent cage. To do that, we have used a series of rare earth and earth abundant photosensitizers that were engaged in either oxidative or reductive excited-state electron transfer processes.[1-5] Cage-escape could be modulated and is some case were shown to increase when the driving force for photo-induced electron transfer increased. Results show that an increase in cage-escape yields from 10% to 60% led to an increase in reaction yields from 30% to over 90%. Current efforts are focused on providing a deeper understanding of these fundamental cage-escape processes.

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Harnessing chirality: molecules, light, properties and applications

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Chirality is a fundamental aspect of Nature, from elementary particles to Chemistry of life. Since early days, chemists have always been fascinating by chirality and they have learned how to prepare and investigate chiral compounds. In recent years, chirality has experienced a new renaissance. Chiral organic materials are founding applications in chiral electronics, e. g. in circularly polarized (CP)-OLEDs, CP-sensitive transistors, spin filters, etc. Such a surge in interest requires the development for new chiral materials and a more complete understanding of structure-property relationships.

In particular, luminescent chiral molecules can emit left and right CP light with different intensities. This phenomenon is called CP luminescence (CPL) and can be exploited both spectroscopically and in various applications. We have developed and investigated purely chiral organic molecules,[1] lanthanide-based chiral coordination compounds[2] and aggregates of chiral small organic molecules in thin films capable of CPL activity.[3] Each class of compounds has peculiar chiroptical properties, arising from their intrinsic nature, and therefore different features and potentialities, which will be discussed during the lecture. Moreover, we have seen that chirality plays a role in spin crossover dynamics in coordination compounds, which can be regulated by controlling the stereochemistry of the complex through chiral anions.[4]

Chirality offers a wide playground for chemists and other scientists, where a true progress can only be achieved through a cooperation among different scientific fields.

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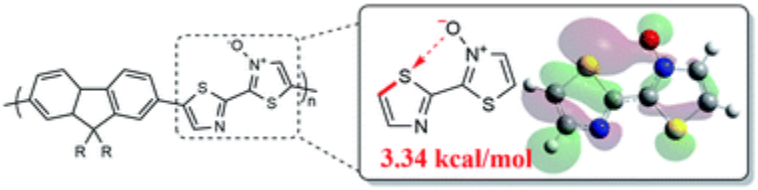
Reaction Development for the Synthesis of Conjugated Organic Materials

Derek J Schipper

Conjugated organic materials are quickly becoming indispensable for technologies such as photovoltaics, light emitting diodes and field-effect transistors. Therefore, efficient assembly of these materials is an important goal. Advancing synthetic strategies provide a direct way to both streamline synthesis and render new architectures synthetically accessible. This talk will discuss our recent efforts developing a C-H bond functionalization and dehydration polymerization strategies to access novel, highly polar, conjugated polymers as well as their resulting properties as low exciton-binding semiconductors.



Electrochemical Deconstructive Functionalization of Cycloalkanols

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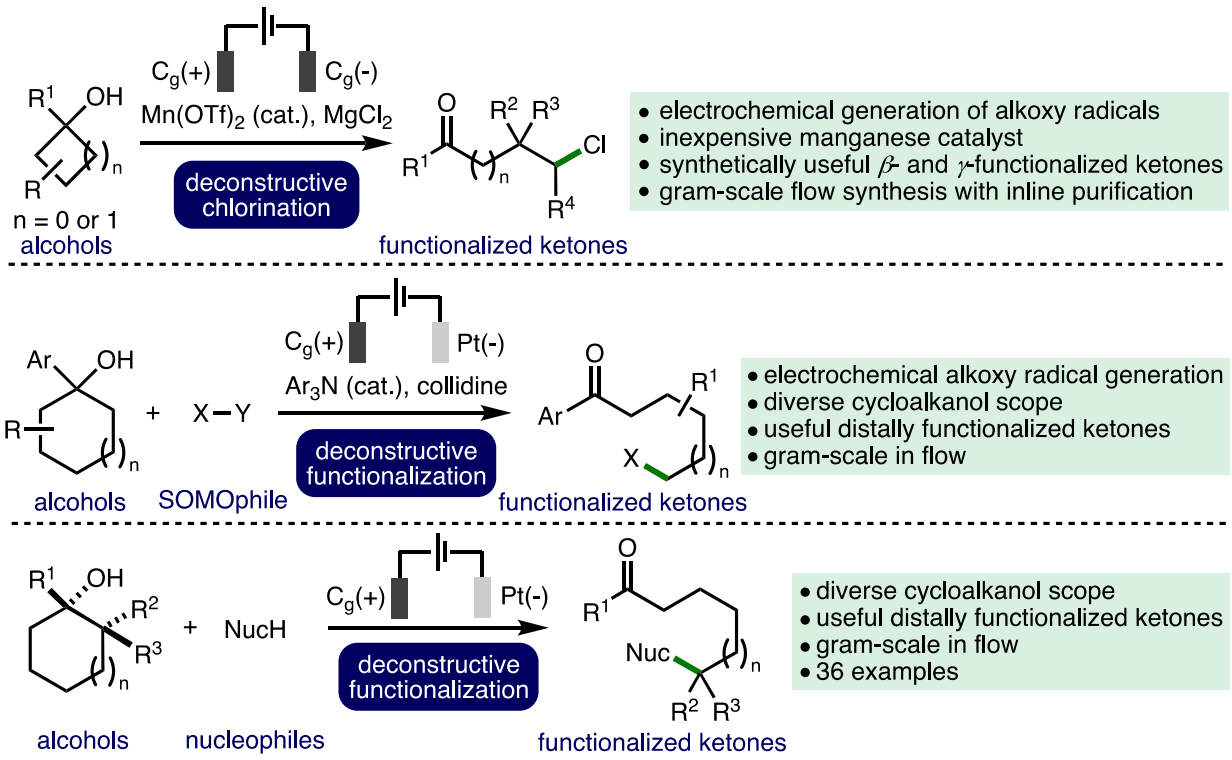
This talk will cover some of our recent research into the development of electrochemical approaches for the deconstructive functionalization of cycloalkanols.[1-3]



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A Radical Approach to Organic Chemistry

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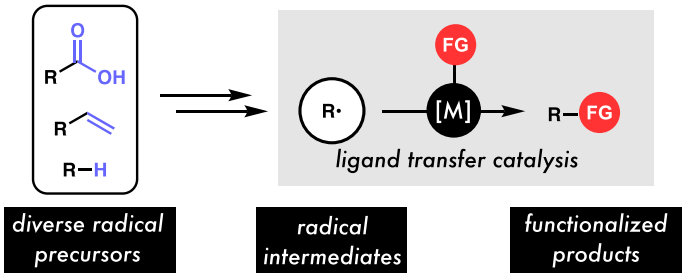
Synthetic chemists need ever better tools to synthesize the molecules of modern life, from life-changing pharmaceuticals to next generation materials. Further, there is increasing need for these transformations to be both step and atom efficient and sustainable, proceeding under mild conditions using earth abundant elements. Here we show how employing open shell intermediates strategically allows for challenging transformations to be achieved directly, from alkene difunctionalization to carboxylic acid deletion [1-3]. Importantly, these reactions make use of earth abundant elements and proceed under mild conditions, with many being driven by light. Together, our studies demonstrate the versatility of radical reactions to achieve challenging disconnections that are sustainable and environmentally-responsible [4].



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Can simple amines mimic organotin?: Aminoalkyl radicals as halogen-atom transfer (XAT) agents for redox chemistry

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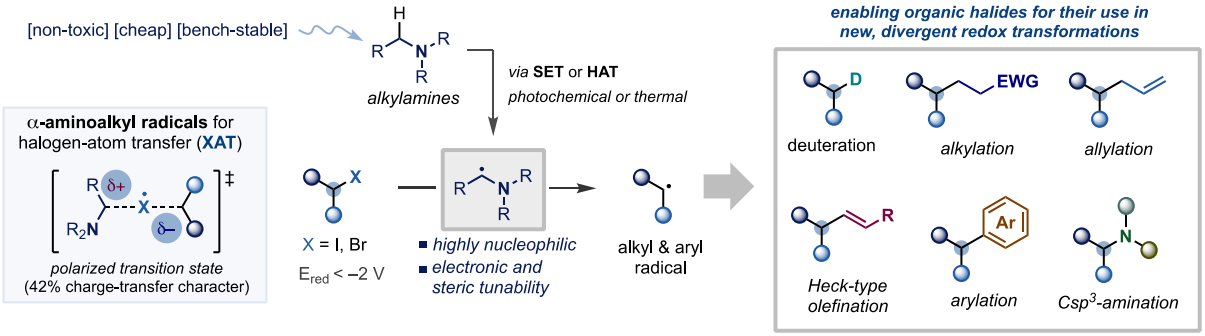
The emergence of (photo)redox catalysis has enabled the development of new methodologies that generate highly reactive radicals under mild conditions [1]. Notwithstanding, the general and reliable generation of carbon radicals from inactivated alkyl and aryl halides remains an unsolved problem in redox chemistry, in view of their often inaccessible SET reduction potentials (E_{red} < –2 V vs SCE) [2]. In fact, nowadays synthetic chemists still rely on the same systems based on halogen-atom transfer (XAT) developed more than 40 years ago to engage organic halides in radical transformations, sometimes underutilized due to the acute toxicity (e.g. tributyltin hydride) or hazards (e.g. explosive initiators) associated to the reagents employed.

We have recently demonstrated how simple amines (*e.g.* triethylamine), some of the cheapest and most common reagents present in any synthetic lab, can be used as surrogates of tributyltin hydride for the homolytic activation of carbon-halogen bonds [3-4]. Aminoalkyl radicals, easily generated under thermal or photochemical conditions from amines, can be engaged in kinetically-favored polarized XAT processes providing effective access to alkyl and aryl radicals. The utility of this strategy has been showcased in a wide range of redox transformations allowing the construction, with high chemoselectivity, of sp^3–sp^3, sp^3–sp^2 and sp^2–sp^2 carbon–carbon and Csp^3–N bonds under mild conditions. Moreover, it has opened a new gateway for the modular use of alkyl and aryl halides in (photo)redox and radical chemistry beyond dehalogenation, further expanding the use of widespread organic halides in redox settings.



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Towards Predictive and Operando Computational Catalysis – Recent Advancements for Transition-Metal Chemistry

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The ultimate goal in computational catalysis is to quantify the factors that govern reactivity and selectivity, enabling the prediction and rational design of superior catalysts. However, the success of such endeavours relies heavily on the accuracy of the chosen computational methodology. Apart from the selection of the electronic structure method, correctly identifying the most stable conformer and considering explicit solute-solvent interactions are crucial for accurately predicting molecular structures, reactivities, and reaction mechanisms.

Yet many current computational studies consider only a single specific conformation, typically derived from experimental data, such as X-ray crystal structure analysis and describe only implicit solvation. This approach starkly contrasts the reality of experimental reaction conditions, where more than one (experimentally derived) conformation can be relevant, and specific solute-solvent interactions can significantly impact reactivity. This discrepancy is particularly problematic when studying transition-metal catalysts, as they can adjust their geometries in response to environmental perturbations.

In my presentation, I will share examples that highlight techniques to enhance the accuracy of computational modelling of transition-metal catalysts. These approaches aim to address explicit solute-solvent interactions [1] and incorporate factors such as conformational diversity,[2-3] counter ions,[4] and reaction dynamics.[5] By integrating these methods, we can significantly improve our ability to predict reactivity and selectivity of reactions catalysed by transition-metal complexes. Ultimately, these techniques contribute to the development of efficient and selective catalysts, a necessity for sustainable processes.

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All-organic Photomagnetic Switching

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Digital data storage relies on the change of a material's electrical, magnetic, or optical properties between two states, indicating 1 and 0. Smaller units of information storage are an interesting research target, because they could lead to higher-density storage. Molecular organic switches are interesting in this context.[1] However, the switching of spin states in all-organic molecules is challenging.
This contribution will focus on a helical photochemical spin-state switch.[2] Configurationally stable dimethyl[5]helicenes were used in the design of a photochemical magnetic switch with bistable spin states (Figure 1).[2] When introducing quinoidal 4,11-substituents, such as oxo or dicyanomethylidene, the helicene undergoes rapid electrocyclization which can be reversed using light as stimulus (77 K). Upon photochemical ring opening at cryogenic temperatures, the helicene favours a diradical configuration with a triplet ground state and a stable EPR signal. The process is fully reversible under thermal conditions and heating (to 93 K for R = C(CN)2 or 127 K for R = O) recovers the diamagnetic closed-shell form via electrocylization. The system can be cycled without any significant degradation and represents a bistable photomagnetic switch that operates under chemical reactivity.
Our current developments indicate that such photomagnetic switching can be highly tuned to different temperature profiles, reaching up to room temperature.

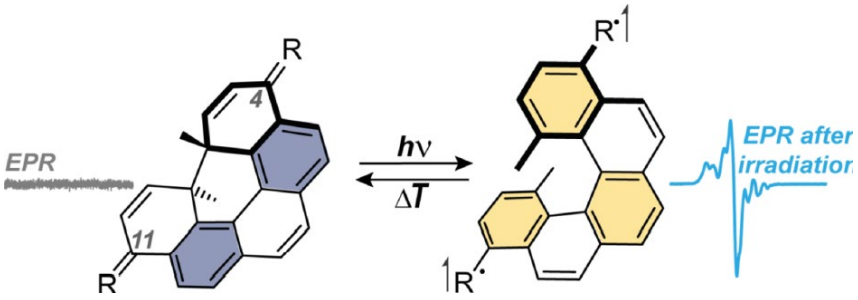

Figure 1. Dimethyl[5]helicene with various 4,11-substituents (R) for photochemical spin-state switching.

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Synthesis of N-Heterocycles via Aryne Intermediates

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Arynes are powerful intermediates in the synthesis of small molecules and pharmaceutically relevant fragments. Despite their useful reactivity, a number of challenges still remain in their use including problems with regioselectivity and the synthesis of N-heterocyclic arynes. Our group has recently been interested in solving both of these challenges and our recent efforts using transition metal-aryne complexes will be discussed.

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