CHIMIA

CHIMIA 2020, Volume 74
ISSN 0009-4293
www. chimia.ch
Supplementa to Issue 7-8/2020

SCS
Swiss Chemical
Society

SCS Fall Meeting 2020 (online conference)
Lecture, Short Talk and Poster Abstracts

Session of Organic Chemistry

August 25, 2020
University of Bern (online conference)
http://scg.ch/fallmeeting/2020

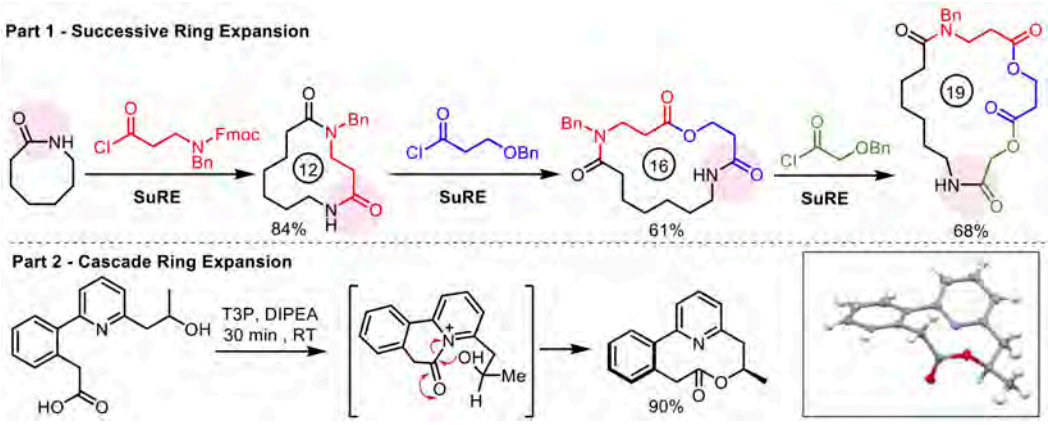
Swiss Chemical Society
Haus der Akademien
Postfach
3001 Bern
Switzerland
info@scg.ch
www.scg.ch

Ring Expansion Approaches for the Synthesis of Functionalised Macrocycles

W. P. Unsworth[1]

[1]University of York, York, YO10 5DD (UK), e-mail: william.unsworth@york.ac.uk

This talk concerns the development of two ring enlargement new way to construct functionalised macrocycles (12+ membered rings) and medium-sized rings (8–11-membered). These ring systems are usually difficult to make, with one of the key challenges being the effective control of intra- and intermolecular reaction during end-to-end cyclisation.[1,2] Both approaches I will discuss in this talk are based on strategies by which the difficult end-to-end cyclisation step can be completely avoided. First, I will describe an iterative ring enlargement approach known as 'Successive Ring Expansion' (SuRE).[3-6] SuRE works be enabling the controlled insertion of amino acid and hydroxy acid fragments into ring enlarged products via a telescoped acylation/rearrangement reaction sequence. Background, methods development, substrate scope/limitations, the synthesis of compound libraries for biological evaluation[4] and DFT calculations[7] will all be covered. Second, a new ring expansion cascade strategy[8,9] will be introduced, that enables the atroposelective synthesis of medium sized rings directly from linear precursors.[10]



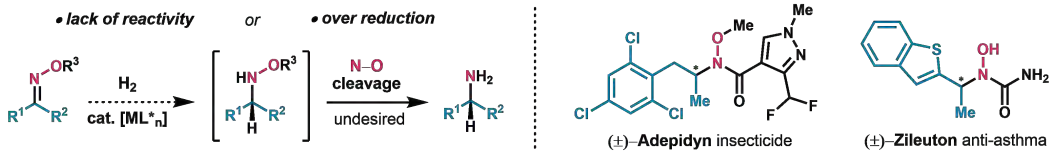
[1] Ring Enlargement in Organic Chemistry, M. Hesse, **1991**, VCH
[2] W. P. Unsworth, J. R. Donald, *Chem. Eur. J.* **2017**, *23*, 8780–8799.
[3] C. Kitsiou, J. J. Hindes, P. I'Anson, P. Jackson, T. C. Wilson, E. K. Daly, H. R. Felstead, P. Hearnshaw, W. P. Unsworth, *Angew. Chem. Int. Ed.* **2015**, *54*, 15794–15798.
[4] L. G. Baud, M. A. Manning, H. L. Arkless, T. C. Stephens, W. P. Unsworth, *Chem. Eur. J.* **2017**, *23*, 2225–2230.
[5] T. C. Stephens, M. Lodi, A. Steer, Y. Lin, M. Gill, W. P. Unsworth, *Chem. Eur. J*. **2017**, *23*, 13314–13318.
[6] T. C. Stephens, A. Lawer, T. French, W. P. Unsworth, *Chem. Eur. J*. **2018**, 24, 13947–13953.
[7] A. Lawer, R. G. Epton, T. C. Stephens, K. Y. Palate, M. Lodi, E. Marotte, K. J. Lamb, J. K. Sangha, J. Lynam, W. P. Unsworth, *Chem. Eur. J*. **2020**, doi: 10.1002/chem.202002164.
[8] T. C. Stephens, W. P. Unsworth, *Synlett* **2020**, 31, 133–146.
[9] A. K. Clarke, W. P. Unsworth, *Chem. Sci.*, **2020**, *11*, 2876–2881.
[10] A. Lawer, J. A. Rossi-Ashton, T. C. Stephens, B. J. Challis, R. G. Epton, J. M Lynam, W. P. Unsworth, *Angew. Chem., Int. Ed*. **2019**, *58*, 13942–13947.

Iridium-catalyzed acid-assisted asymmetric hydrogenation of oximes to hydroxylamines

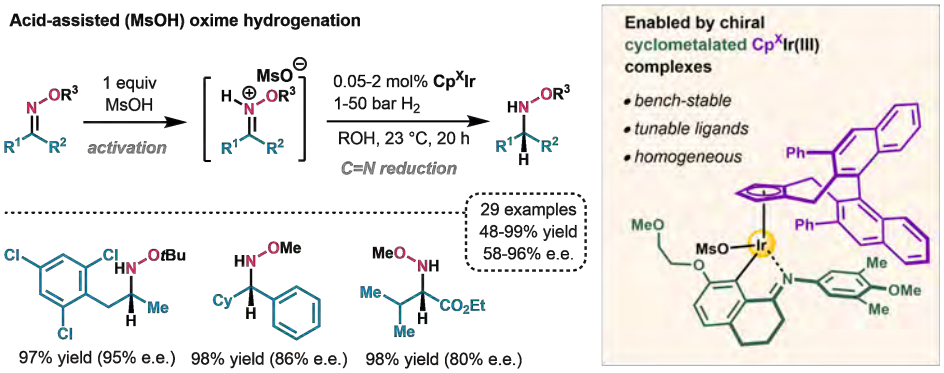
J. Mas-Roselló[1], T. Smejkal[2], N. Cramer[1]*

[1]EPFL Lausanne, Switzerland, [2]Syngenta Crop Protection AG, Stein, Switzerland

Asymmetric hydrogenation with homogeneous transition metal-catalysts is one of the most efficient methods for the synthesis of chiral building blocks at industrial scale.[1] The selective reduction of an oxime to the corresponding chiral hydroxylamine derivative remains elusive. These substrates are often inert, and when reactivity is observed, undesired reductive cleavage of the labile N–O bond leads to primary amines.[2] Current bioactive N–O compounds (e.g. Adepidyn, Zileuton) are marketed as racemates. A practical asymmetric synthesis would facilitate incorporation of chiral 3D hydroxylamine scaffolds as design elements in drug discovery.



We developed a robust cyclometalated iridium(III) complex bearing a chiral cyclopentadienyl ligand (Cp^X) as an efficient catalyst for oxime hydrogenation under highly acidic conditions.[3] The reaction is fully chemoselective towards reduction of the C=N bond, showing no cleavage of the N–O bond. Valuable *N*-alkoxy amines can be accessed at room temperature in catalyst turnover numbers up to 4000 and enantiomeric ratios up to 98:2. These findings may inspire future metal-catalyzed enantioselective hydrogenations of challenging substrates.



[1] David J. Ager, André H. M. de Vries, Johannes G. de Vries, *Chem. Soc. Rev.*, **2012**, 41, 3340-3380.
[2] Anna M. Maj, Isabelle Suisse, Francine Agbossou-Niedercorn, *Tetrahedron: Asymmetry*, **2016**, 27, 268-273.
[3] Josep Mas-Roselló, Tomas Smejkal, Nicolai Cramer, *Science*, in press.

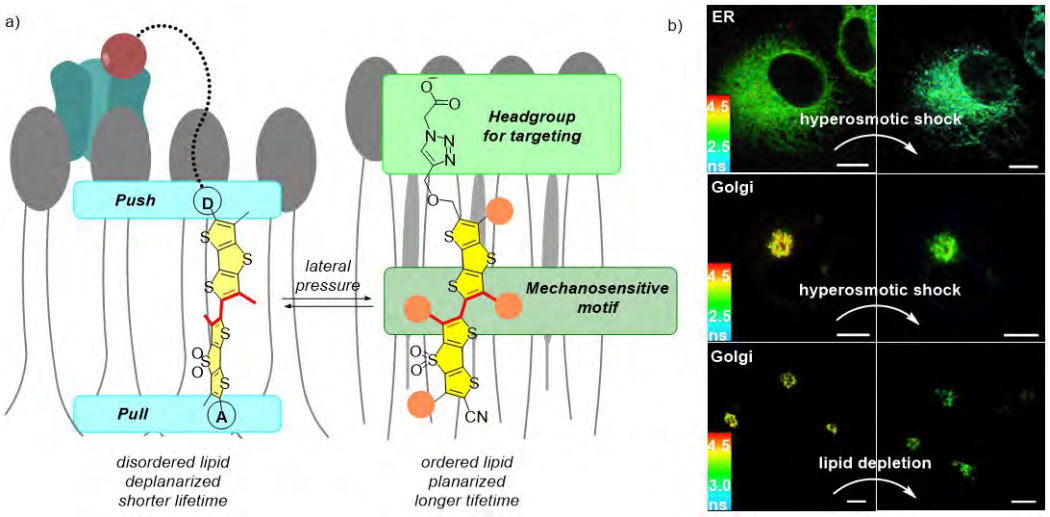
Fluorescent Probes to Image Physical Forces in Living Cells

K. Strakova[1,4], J. López-Andarias[1,4], G. Licari[2], A. Colom[3,4], N. Jiménez-Rojo[3,4], E. Tajkhorshid[2], A. Roux[3,4], H. Riezman[3,4], N. Sakai[1], S. Matile[1,4]*

[1]Department of Organic Chemistry, University of Geneva, Switzerland, [2]Center for Biophysics and Quantitative Biology, University of Illinois at Urbana-Champaign, USA, [3]Biochemistry Department, University of Geneva, Switzerland, [4]National Centre of Competence in Research (NCCR) Chemical Biology

Aiming to provide better understanding of forces ruling in biological membranes, mechanosensitive “flipper” probes have been developed. These fluorescent push-pull dimers respond to varying forces in membranes by a combined effect of ground state planarization and polarization, thus giving a direct fluorescent readout of changes in tension and lipid order of the surrounding membrane [1,2].

In past few years, our attention has been focused mainly on a) improving the spectroscopic and mechanical properties of the dye and b) attaching targeting groups to specifically reach desired cellular sites. By tailoring our flippers almost atom by atom, we have gained insight on the relationship between twist/push-pull strength and mechanosensitivity [3,4]. More importantly for biology, by attaching classical targeting motifs [5], or exploiting protein tag strategies [6], we have been able to specifically stain membranes of various cellular organelles and report successfully on their lipid order and membrane tension changes induced by different means.



[1] K. Strakova, L. Assies, A. Goujon, F. Piazzolla, H. Humeniuk, S. Matile, *Chem. Rev.* **2019**, *119*, 10977–11005.
[2] G. Licari, K. Strakova, S. Matile, E. Tajkhorshid, *Chem. Sci.* **2020**, *in press.*
[3] K. Strakova, A. Poblador-Bahamonde, N. Sakai, S. Matile, *Chem. Eur. J.* **2019**, *25*, 14935–14942.
[4] M. Macchione, N. Chuard, N. Sakai, S. Matile, *ChemPlusChem*, **2017**, 82, 1062–1066.
[5] A. Goujon, A. Colom, K. Strakova, V. Mercier, D. Mahecic, S. Manley, N. Sakai, A. Roux, S. Matile, *Am. Chem. Soc.* **2019**, *141*, 3380–3384.
[6] K. Strakova, J. López-Andarias, N. Jiménez-Rojo, J. Chambers, S. J. Marciniak, H. Riezman, N. Sakai, S. Matile, *submitted.*

Assessment of the Synthetic Feasibility of Generated Chemical Space by Computer Assisted Synthesis Planning

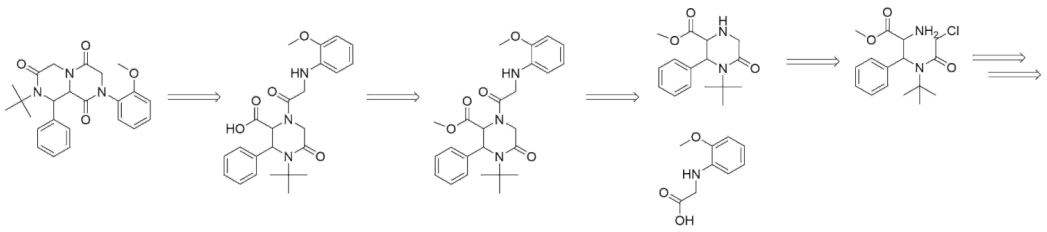
A. Thakkar[1], V. Chadimova[2], E. J. Bjerrum[2], O. Engkvist[2], J. L. Reymond[1]*

[1]Department of Chemistry and Biochemistry, Freiestrasse 3, 3012 Bern, [2]Hit Discovery, Discovery Sciences, R&D, AstraZeneca, Gothenburg, Sweden

Computer assisted synthesis planning has gained considerable interest in recent years owing to the resurgence of artificial intelligence (AI), and the prospect of accelerating the discovery and synthesis of new chemical entities.[1] Our previous work highlights the implementation of a retrosynthetic prediction tool trained on the largest collection of datasets to date, and demonstrates its applicability to a set of compounds obtained from virtual libraries.[2] Additionally, we have further augmented our CASP tool with a model called 'Ring Breaker' to assess synthetic disconnections for complex ring systems.[3] This model is trained specifically for ring forming reactions and is used to augment the search for synthetic pathways by identifying routes that utilise ring formations. To maximise the number of synthetic options during the search for synthetic pathways, we further augment the model with an applicability filter, which informs the model which reactions are applicable *in silico*.

In this study, we build upon our previous work in computer aided synthesis planning (CASP) by tackling the problem of synthetic accessibility.[2, 3] The improvements to our baseline retrosynthetic tool allow for a better estimation of the synthetic feasibility of a diverse set of compounds obtained from ChEMBL, GDBChEMBL, GDBMedChem and Drugbank, as determined by running full retrosynthetic predictions. The outcomes of the retrosynthetic predictions are used as an estimate for synthetic feasibility and are used to train a variety of machine/deep learning models that can be used as a surrogate to the prediction of full synthetic routes. The resulting surrogate model can be used to score the synthetic accessibility of a diverse set of generated compounds from virtual libraries or used in the generation process to maximise the synthetic feasibility of compounds.

AI generated route for the bicyclic piperazine



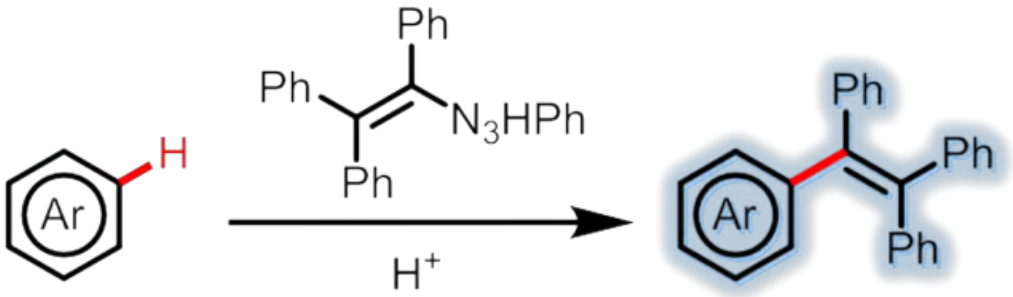
[1] Jensen, K. F.; Coley, C. W.; Eyke, N. S., Autonomous discovery in the chemical sciences part I: Progress. *Angewandte Chemie International Edition* **2019**.
[2] Thakkar, A.; Kogej, T.; Reymond, J.-L.; Engkvist, O.; Bjerrum, E. J., Datasets and their influence on the development of computer assisted synthesis planning tools in the pharmaceutical domain. *Chemical Science* **2020,** *11* (1), 154-168.
[3] Thakkar, A.; Selmi, N.; Reymond, J.-L.; Engkvist, O.; Bjerrum, E. J., 'Ring Breaker': Neural Network Driven Synthesis Prediction of the Ring System Chemical Space. *ChemRxiv* **2020**.

Synthesis of Tetraarylethene Luminogens by C-H Vinylation of Arenes

A. A. Suleymanov[1], K. Severin[1]*

[1]Ecole Polytechnique Fédérale de Lausanne

Compounds showing aggregation-induced emission (AIE) properties have found numerous applications in analytical chemistry, imaging, materials sciences, and biology. Tetraarylethenes are particularly popular in this context. During our investigations of the chemistry of vinyl triazenes,[1-4] we have developed a novel route towards tetraarylethene AIE emitters via metal-free C-H triarylvinylation of aromatic compounds with vinyl triazenes.[5] The scope of the coupling reaction includes simple unactivated arenes, functional arenes, heteroarenes and aromatic polymers. Within the course of this study, we have accidentally found a new class of solid state emitters based on Δ^3-triazolines.[6] These molecules display electrofluorochromism: it is possible to convert them reversibly into stable non-fluorescent radical cations.



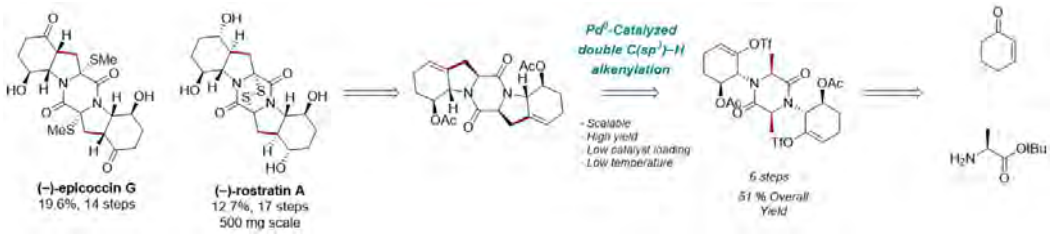
[1] D. Kossler, F. Perrin, A. A. Suleymanov, G. Kiefer, R. Scopelliti, K. Severin, N. Cramer, *Angew. Chem. Int. Ed.* **2017**, *56*, 11490.
[2] A. A. Suleymanov, R. Scopelliti, F. Fadaei-Tirani, K. Severin, *Org. Lett.* **2018**, *20*, 3323.
[3] A. A. Suleymanov, R. Scopelliti, F. Fadaei-Tirani, K. Severin, *Adv. Synth. Catal.* **2018**, *360,* 4178.
[4] A. A. Suleymanov, E. Le Du, Z. Dong, B. Muriel, R. Scopelliti, F. Fadaei-Tirani, J. Waser, K. Severin, *Org. Lett.* **2020**, 10.1021/acs.orglett.0c01527.
[5] A. A. Suleymanov, M. Doll, A. Ruggi, R. Scopelliti, F. Fadaei-Tirani, K. Severin, *Angew. Chem. Int. Ed.* **2020**, 10.1002/anie.201908755.
[6] A. A. Suleymanov, A. Ruggi, O. M. Planes, A.-S. Chauvin, R. Scopelliti, F. Fadaei-Tirani, A. Sienkiewicz, A. Fabrizio, C. Corminboeuf, K. Severin, *Chem. Eur. J.* **2019**, *25*, 6718.

Divergent Total Synthesis of (−)-epicoccin G and (−)-rostratin A Enabled by Double C(sp^3)−H Activation

P. Thesmar[1], O. Baudoin[1]*

[1]Department of Chemistry, University of Basel, Switzerland

Dithiodiketopiperazine (DTP) natural products comprise a large number of metabolites, which display a wide range of biological activities including antiviral, antibacterial, antiallergic, antimalarial and cytotoxic properties.[1] DTPs, characterized by sulfur atoms on a fused diketopiperazine (DKP) structure, have gained significant interest from the synthetic community, due to their unique structural and biological properties. In particular, the groups of Nicolaou, Reisman and Tokuyama have reported elegant total syntheses of DTP molecules containing a symmetrical pentacyclic ring system.[2,3,4] The innovative strategy reported herein is based on a Pd^0-catalysed double C(sp^3)−H alkenylation key step allowing straightforward, high-yielding and concise access to a common advanced intermediate bearing the pentacyclic DKP scaffold.[5,6] The latter can be readily derivatised into several DTP natural products.



Herein, we report the application of this C(sp^3)–H activation-based strategy to the enantioselective, scalable and divergent synthesis of (−)-epicoccin G and (−)-rostratin A, which are synthesized for the second and first time, respectively.[7,8] Moreover, in reason of their interesting cytotoxic properties, biological assays are currently undergoing on (−)-rostratin A and closely related analogues.

[1] A. D. Borthwick, *Chem. Rev*. **2012**, *112*, 3641−3716.
[2] K. C. Nicolaou and al, *J. Am. Chem. Soc.* **2012**, *134*, 17320–17332.
[3] J. A. Codelli, A. L. A. Puchlopek and S. E. Reisman, *J. Am. Chem. Soc.* **2012**, *134,* 1930–1933
[4] H. Fujiwara, T. Kurogi, S. Okaya, K. Okano and H. Tokuyama, *Angew. Chem., Int. Ed.*, **2012**, *51*, 13062–13065.
[5] O. Baudoin, *Acc. Chem. Res.*, **2017**, *50* (4), 1114–1123
[6] D. Dailler, G. Danoun, O. Baudoin, *Angew. Chem. Int. Ed.* **2015**, *54*, 4919-4922
[7] P. Thesmar, O. Baudoin, *J. Am. Chem. Soc*. **2019**, *141*, 15779−15783.
[8] P. Thesmar, S. Coomar, A. Prescimone, D. Gillingham, O. Baudoin, *manuscript in preparation*.

Recent Case Study by Janssen R&D

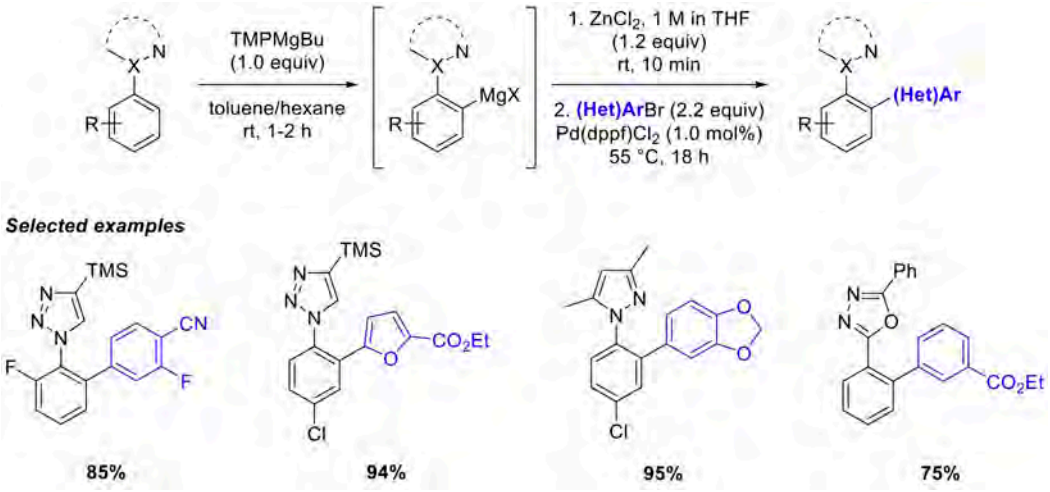
S. Wagschal[1]

[1]Janssen Pharmaceutica - swagscha@its.jnj.com

Simon Wagschal,[a] Diego Broggini,[a] Tobias Strittmatter,[a] Trung Duy Chi Cao,[a] Luca Perego,[a] Pascal Schleiss,[a]Kristian Paun,[a] Jessica Steiner,[a] Anna-Lena Merk,[a] Joachim Harsdorff,[a] Sven Hock,[a] Elena Cosimi,[a] Stefan Schirling,[a] Jan Dijkmans,[b] Brecht Egle,[b] Sébastien Lemaire,[b] Ferdinand H. Lutter,[c] Lucie Grokenberger,[c] Paul Knochel[c] and Roger Fässler[a]

[a] Discovery Product Development and Supply, Janssen Pharmaceutica, Hochstrasse 201, 8200 Schaffhausen (Switzerland), [b] Discovery Product Development and Supply, Janssen Pharmaceutica, Turnhoutseweg 30, B-2340 Beerse (Belgium), [c] Ludwig-Maximilians-Universität München, Department Chemie, Butenandtstrasse 5-13, Haus F, 81377 München (Germany)

Aryl azole scaffolds are present in a wide range of pharmaceutically relevant molecules. Their ortho-selective metalation at the aryl ring is challenging, due to the competitive metalation of the more acidic heterocycle. Seeking a practical access to a key Active Pharmaceutical Ingredient (API) intermediate currently in development, we investigated the metalation of 1-aryl-1,2,3-1*H*-triazoles and other related heterocycles with sterically hindered metal amide bases. We report here a room-temperature and highly regioselective ortho magnesiation of several aryl azoles using a new tailored magnesium amide, TMPMgBu (TMP = 2,2,6,6-tetramethylpiperidyl) in hydrocarbon solvents followed by an efficient Pd-catalyzed arylation. This scalable and selective reaction allows variation of the initial substitution pattern of the aryl ring, the nature of the azole moiety, as well as the nature of the electrophile. This versatile method can be applied to the synthesis of bioactive azole derivatives and complements existing metal-mediated ortho-functionalizations.



[1] F. H. Lutter, L. Grokenberger, L. A. Perego, D. Broggini, S. Lemaire, S. Wagschal, P. Knochel, *submitted*.

Understanding Catalysis in Iron Heme Metalloproteins Using Non-Canonical Amino Acids

M. Tinzl[1], T. Hayashi[1], M. Pott[1], U. Krengel[2], J. Proppe[1], J. Soetbeer[1], D. Klose[1], M. Reiher[1], G. Jeschke[1], D. Hilvert[1]*

[1]ETH Zürich, [2]University of Oslo

Non-canonical amino acid ligands are useful for fine-tuning the catalytic properties of metalloenzymes. We showed that recombinant replacement of the histidine ligand proximal to heme in myoglobin with N_δ-methylhistidine enhances the protein's promiscuous carbene transfer chemistry, enabling efficient styrene cyclopropanation in the absence of reductant, even under aerobic conditions[1]. The mutant protein's reduced sensitivity to oxygen enabled us to capture and characterize a reactive carbenoid adduct by UV/vis spectroscopy, EPR spectroscopy and X-ray crystallography. Together with another structure recently published by the Arnold group[2], these two structures represent the first carbenoid structures characterized in a protein. Elaborating on this approach, we further expanded the panel of histidine analogs accessible for incorporation into proteins via stop codon suppression. These analogs include 4- and 5-thiazolyl alanine as well as 3-thienyl alanine which can coordinate the iron heme either via nitrogen or sulfur. Characterization of the reactivity of these proteins in three carbene transfer model reactions– N-H insertion, S-H insertion and cyclopropanation– shows that the non-canonical amino acid 5-thiazolyl alanine is a privileged proximal ligand, as the corresponding myoglobin derivatives outperform other enzymes under most tested reaction conditions. Our findings suggest that Fe(III) catalysis is possible in carbene transfer reactions catalyzed by iron heme proteins, previously Fe(II) catalysis was the most widely accepted mechanistic proposition. Overall, our studies show that non-canonical amino acids can enhance catalytic performance, enable novel chemistries and reveal reactive intermediates.

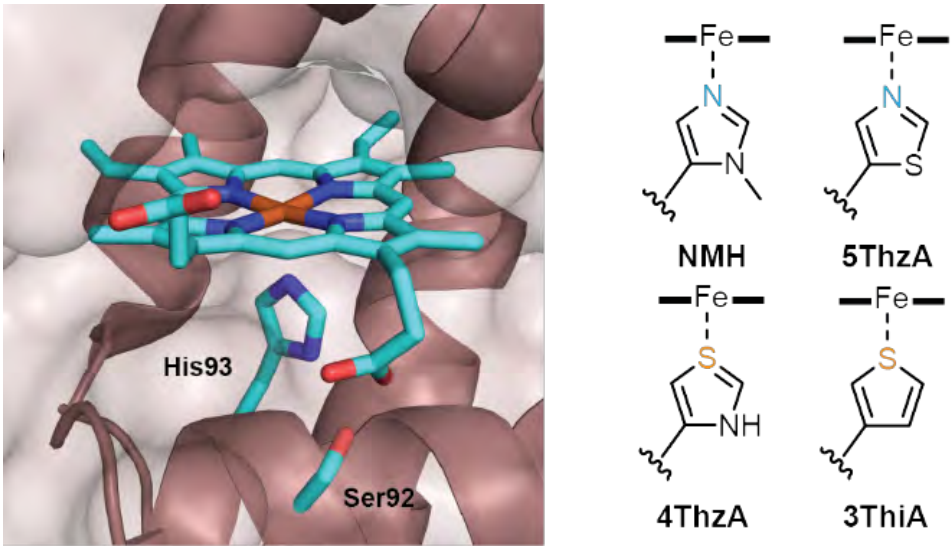


Fig: Active site of myoglobin showing ligation of the heme cofactor by His93. Non canonical amino acids incorporated in place of histidine are N_δ-methylhistidine (NMH), 5-thiazolyl alanine (5Thz), 4-thiazolyl alanine (4Thz) and 3-thienyl alanine (3ThiA).

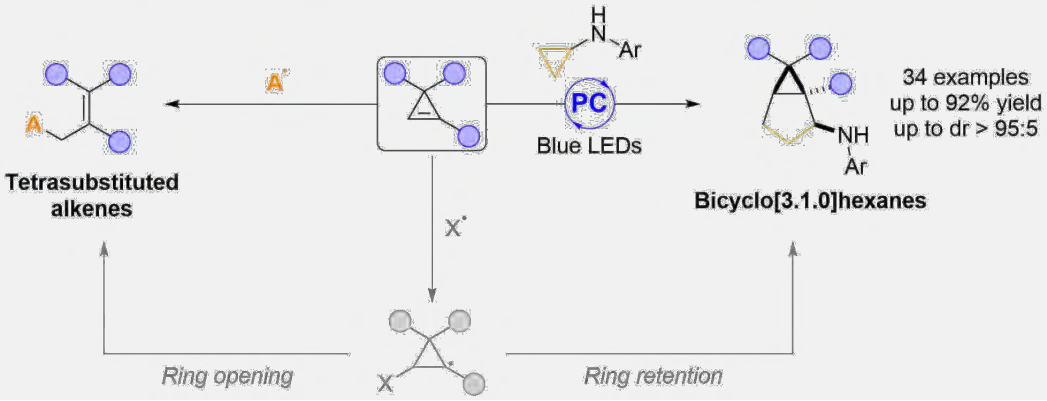
[1] Takahiro Hayashi, Matthias Tinzl, *et al., Nature Catalysis,* **2018**, 1, 578–584.
[2] Russel D. Lewis, *et al., Proceedings of the National Academy of Sciences,* **2011**, 115, 7308–7313

Radical Functionalization of Cyclopropenes for the Synthesis of Bicyclo[3.1.0]hexanes and Substituted Alkenes

B. Muriel[1], A. Gagnebin[1], J. Waser[1]*

[1]Laboratory of Catalysis and Organic Synthesis (LCSO), Institute of Chemical Sciences and Engineering (ISIC), EPFL

In the last two decades, cyclopropenes have been widely used as highly reactive three-carbon building blocks to access diverse chemical motifs. [1] Compared to carbometallation reactions and transition metal-mediated processes, [2] the use of radical chemistry to functionalize the double bond of cyclopropenes has not been much investigated so far, despite its high synthetic potential. [3] Herein, we report two new transformations based on the radical functionalization of cyclopropenes. The first proceeds with retention of the three-membered ring, involving a photoredox-mediated (3+2) annulation with cyclopropylanilines. This process provides a new and convergent strategy towards diastereomerically enriched and highly substituted bicyclo[3.1.0]hexanes, which are important scaffolds in medicinal chemistry. [4] In addition, our latest results for the synthesis of tetrasubstituted alkenes by a radical functionalization of cyclopropenes followed by ring opening, will be presented. [5] Discussion about this research will be also possible during a zoom meeting on Tuesday 25.08.2020, 12:15-13:15. [6]



[1] R. Vincente, *Synthesis*, **2016**, 48, 2343-2360.
[2] Z. Zhu, Y. Weib, M. Shi, *Chem. Soc. Rev.*, **2011**, 40, 5534-5563.
[3] N. S. Dange, F. Robert, Y. Landais, *Org. Lett.*, **2016**, 18, 6156-6159.
[4] B. Muriel, A. Gagnebin, J. Waser, *Chem. Sci.*, **2019**, 10, 10716-10722.
[5] B. Muriel, J. Waser, *Manuscript in preparation.*
[6] The link will be available on the following document shortly before:
https://drive.google.com/file/d/1s1Tg48ABj5q010FyUV29sckTHGopQv6o/view?usp=sharing

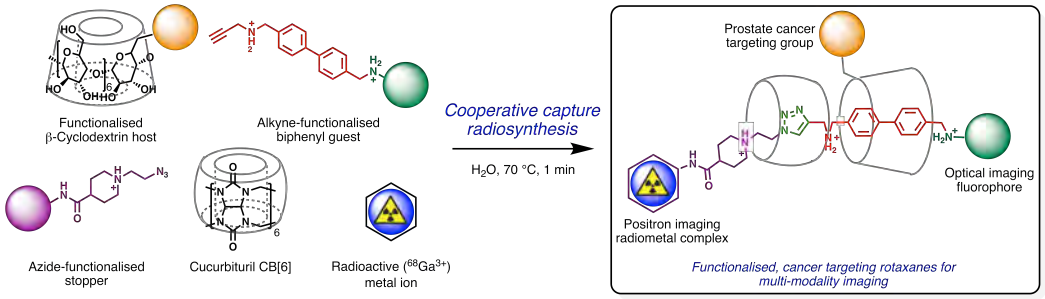
A multi-modality platform to develop supramolecular radiopharmaceuticals

F. D'Orchymont[1], J. P. Holland[1]*

[1]University of Zurich, Department of Chemistry, Zurich, Switzerland

Supramolecular chemistry involves systems held together by non-covalent interactions. These systems hold promise in the design of drug delivery systems targeting cancer. Our goal is to use the supramolecular chemistry of rotaxanes as a scaffold for building multi-modality imaging agents. To this end, we report the synthesis and characterisation of functionalised, cancer targeting radiotracers.

A cooperative capture approach was used to develop radiolabelled, mechanically interlocked molecules (rotaxanes). Our attention focused on a 'click' chemistry reaction involving triazole formation by catalysis using CB[6] and β-CD. An efficient preorganisation between the azide and alkyne derivatives, CB[6] and β-CD via hydrogen bonds, facilitated a rapid synthesis of rotaxanes functionalised with metal ion complexes, fluorophores and cancer-specific ligands. The monofunctionalisation of β-CD also expand the versatility of the construct. To demonstrate the flexibility of our design, we synthesised various radioactive rotaxanes in a one-pot strategy. Thus, ^{68}Ga-desferrioxamine or ^{68}Ga-NODAGA complexes, fluorescein and Lys-NHC(O)NH-Glu inhibitors were used as stoppers on the axels of the rotaxanes or as functional features on the β-CD macrocycle. Reactions to make multi-functional rotaxanes were complete in less than one minute at 70 °C in biologically compatible media. All constructs were characterised by multinuclear NMR, high-resolution electrospray ionisation mass spectrometry and high-performance liquid chromatography. Radiolabelling reactions gave ^{68}Ga-rotaxanes in high radiochemical yield and purity. To the best of our knowledge, this work represents the first use of supramolecular chemistry to access cancer-specific radiotracers for multi-modality imaging. Biological studies including cellular uptake and binding assays, and PET imaging in mouse models of human cancer, are underway.



[1] M. Webber, R. Langer, *Chem. Soc. Rev.*, **2017**, *46*, 6600-6620.
[2] W. L. Mock, T. A. Irra, J. P. Wepsiec, T. L. Manimaran, *J. Org. Chem.*, **1983**, *48*, 3619-3620.
[3] X. Hou, C. Ke, J. F. Stoddart, *Chem. Soc. Rev.*, **2016**, *45*, 3766-3780.

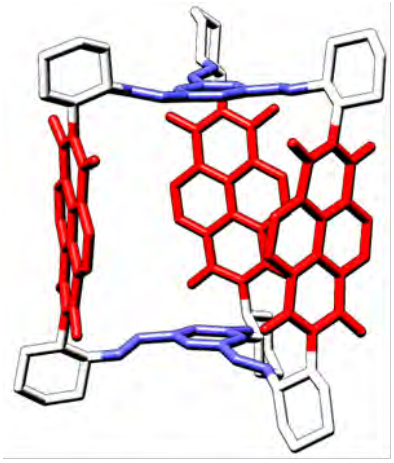
Synthesis of chiral and redox-active covalent organic cages

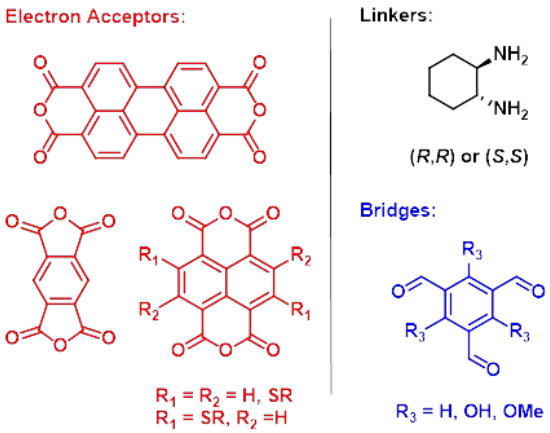
H. Huang[1], T. Šolomek[1]*

[1]Department of Chemistry, University of Basel, St. Johanns-Ring 19, 4056 Basel, Switzerland

Porous organic materials have been discovered roughly a decade ago but rapidly developed because they possess several attractive features as gas storage or separation materials.[1-2] For example, porous organic cages have an intrinsic cavity and can be crystallized with permanent voids that allow access for guest molecules to get adsorbed inside the crystal. These types of molecules can, therefore, behave like a zeolite because of the porosity but offer processability typical for organic compounds.

Porous organic cages are typically assembled by dynamic covalent chemistry[3] (DCC) that allows for error correction in the cage formation. Recently, we have synthesized a series of chiral covalent organic cages with three built-in redox-active rylene-based units by dynamic imine chemistry.[4] Structural characterizations were carried out via NMR and single-crystal X-ray diffraction, which demonstrated the three-dimensional structure prevents the three redox-active units from aggregation. The structure of these cages allowed us to investigate their properties in applications, such as gas adsorption and separation with promising results. This contribution will reveal our early achievements and will discuss our findings regarding the formation of the rylene cages and their new exciting derivatives. Our investigations show a great potential of our organic cages in applications beyond the host-guest chemistry.





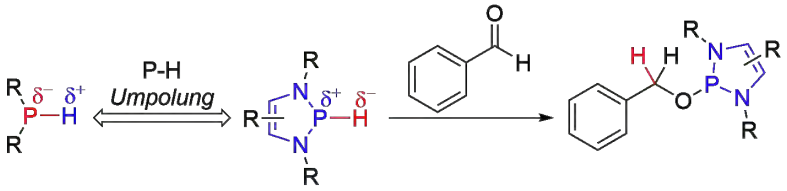
[1]Tom Hasell, Andrew I. Cooper, *Nature Reviews*, **2016**, *1*, 1-14.
[2]Florian Beuerle, Bappadity Gole, *Angewandte Chemie International Edition*, **2018**, 57, 4850-4878.
[3]Mathew E. Belowich, J. Fraser Stoddart, *Chemical Society Reviews*, **2012**, *41*, 2003-2024.
[4] a.) Tomáš Šolomek, Natalia E. Powers-Riggs, Yi-Lin Wu, Ryan M. Young, Matthew D. Krzyaniak, Noah E. Horwitz, Michael R. Wasielewski, *Journal of the American Chemical Society*, **2017**, *139*, 3348-3351.; b.) Hsin-Hua Huang, Kyung Seob Song, Alessandro Prescimone, Rajesh Mannancherry, *Ali Coskun*, Tomáš Šolomek, *manuscript in preparation*.

Polar Opposites in Phosphorus Catalysis: Applications of 1,3,2-Diazaphospholenes

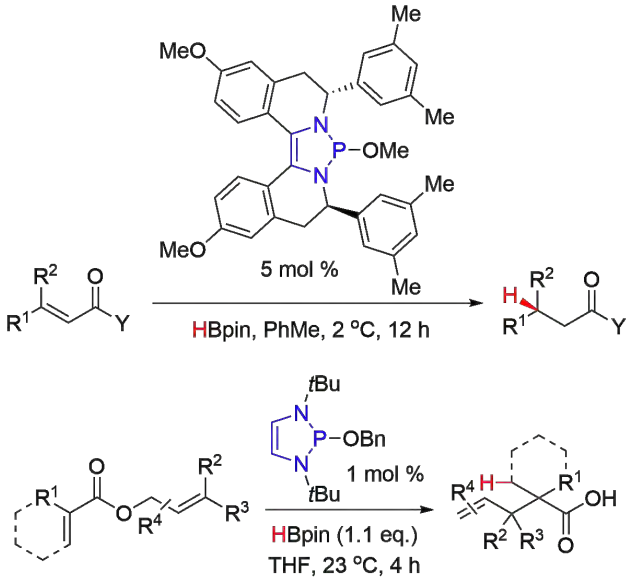
J. Reed[1], N. Cramer[1]*

[1]Laboratory of Asymmetric Catalysis and Synthesis, EPF Lausanne

Phosphorus based catalysts have, in recent years, received considerable attention from the synthetic organic chemistry community as a result of their unique and interesting reactivity, and their superior economic and ecological profiles when compared to transition-metal based catalysts. 1,3,2-Diazaphospholenes (DAPs) are a particular class of catalysts that offer orthogonal reactivity to more canonical phosphorus based catalysts (Figure 1).[1] The significant delocalisation of electrons around the heterocyclic core leads an Umpolung of the P-H bond, resulting in the most powerful hydride donor quantified on the Mayr nucleophilicity scale.[2]



We have exploited this remarkable property of the DAPs to develop a range of catalytic reductive methodologies: a bespoke chiral DAP enabled the highly enantioselective conjugate reduction of a wide variety of α,β-unsaturated carbonyl compounds (Figure 2),[3] while the transient phosphorus enolate that is generated in this process could be exploited to generate C-C bonds through a [3,3]-sigmatropic rearrangement.[4] Examination of the solid-state single crystal X-ray diffraction analysis in combination with detailed NMR studies have shed light on mechanism by which these catalysts operate, as well as providing a blueprint for future developments in this field.



[1] Dietrich Gudat, Asadolla Haghverdi, Martin Nieger, *Angew. Chem. Int. Ed.* **2000**, *39*, 3084–3086.
[2] Jingjing Zhang, Jin-Dong Yang, Jin-Pei Cheng, *Angew. Chem. Int. Ed.* **2019**, *58*, 5983–5987.
[3] Solène Miaskiewicz*, John H. Reed*, Pavel A. Donets, Caio C. Oliveira, Nicolai Cramer, *Angew. Chem. Int. Ed.* **2018**, *57*, 4039–4042.
[4] John H. Reed, Pavel A. Donets, Solène Miaskiewicz, Nicolai Cramer, *Angew. Chem. Int. Ed.* **2019**, *58*, 8893-8897.

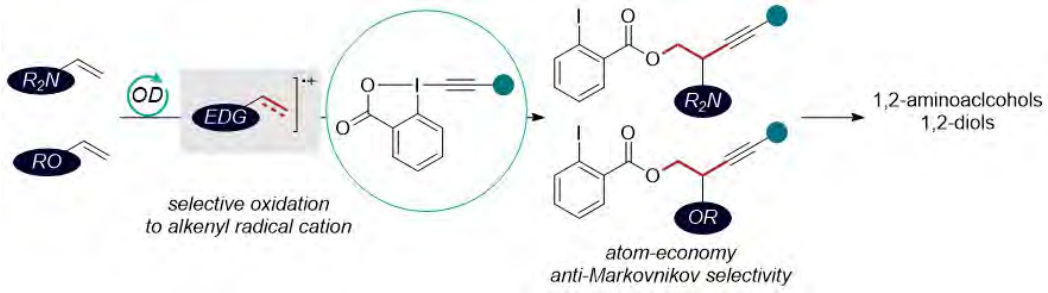
Anti-Markovnikov Oxyalkynylation of Ene-carbamates and Enol-ethers under Photoredox Catalysis

S. G. Amos[1], S. Nicolai[2], J. Waser[3]*

[1]Laboratory of Catalysis and Organic Synthesis, EPFL Lausanne, [2]Laboratory of Catalysis and Organic Synthesis, [3]Laboratory of Catalysis and Organic Synthesis (LCS

Atom economy constitutes a key point of interest for new synthetic methodologies. Alkene difunctionalisation is, in this context, an excellent example. It allows a rapid increase of molecular complexity, in particular in radical transformations.[1] Over the past decades, photocatalysis has emerged as a selective and efficient way to generate reactive radical intermediates.[2] In recent years, the scope of atom transfer radical additions (ATRA) to alkenes has been extended under photocatalytic conditions, allowing them to take place under mild conditions at room temperature.[3]

Alkynes have broad applications and are highly useful platforms for subsequent reactions. The development of new alkynylation strategies has become a major research topic in our group. Herein, we present a new metal-free photocatalytic method for the selective difunctionalisation of ene-carbamates and enol-ethers passing through a radical cation intermediate. This methodology exploits the somophilic character of the EthynylBenziodoXolone (EBX) reagents to allow the atom economical oxyalkynylation of alkenes providing acetylene containing 1,2-aminoalcohols and 1,2-diols.[4], [5]



[1] M. P. Plesniak, H.-M. Huang, D. J. Procter, *Nat. Rev. Chem.* **2017**, *1*, 0077.
[2] C. K. Prier, D. A. Ranic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322-5363.
[3] T. Courant, G. Masson, *J. Org. Chem.* **2016**, 81, 6945-6952.
[4] S. G. E. Amos, S. Nicolai, J. Waser, *Manuscript in preparation.*
[5] Discussion about this research will be possible during a zoom meeting on Tuesday 25.08.2020, 12:15-13h15. The link will be available on the following document shortly before:
https://drive.google.com/file/d/1s1Tg48ABj5q010FyUV29sckTHGopQv6o/view?usp=sharing

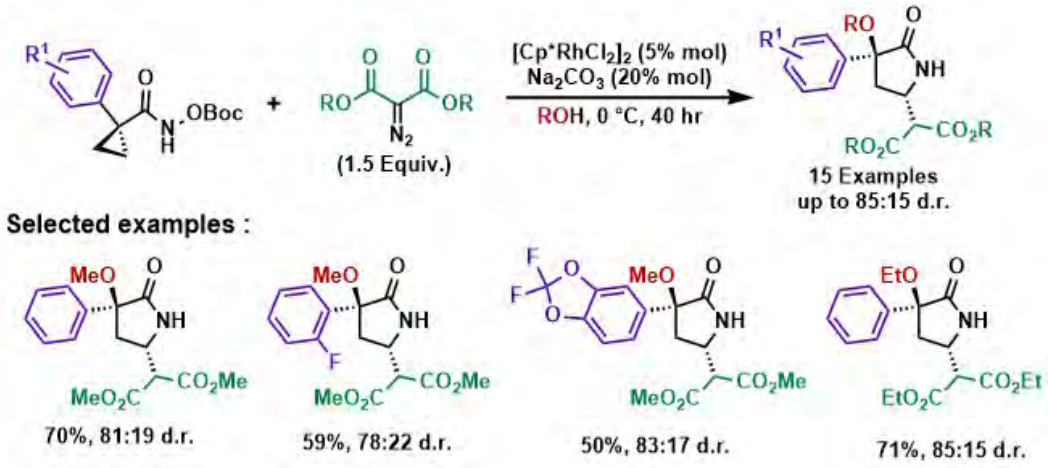
A Rhodium(III)-Catalyzed Cyclopropane C-H/C-C Activation Sequence Provides Diastereoselective Access to α-Alkoxylated γ-Lactams

B. Audic[1], N. Cramer[1]*

[1]EPFL Lausanne, Switzerland

The cyclopentadienyl (Cp) ligand and its pentamethylsubstituted derivatives are of fundamental importance in organometallic chemistry.[1] Cp complexes are known for most transition metals, and have been widely applied in numerous catalytic processes, notably for C-H functionalization transformations. However, to date, only one example[2] exploit the potential of Cp*Rh(III) catalysts for C-C bond cleavage of strained ring.[3]

Heterocycles are very important structural, among them γ-lactams are ubiquitous in many biologically active natural products and pharmaceuticals.[4] Herein, we present an unprecedented synthesis of highly substituted pyrrolidinone (**Figure 1**), a precursor to pyrrole heterocycles. The developed transformation rely on a multicomponent process under mild conditions. Furthermore, examination of side-products structures combine with control experiments have shed light on the operative mechanism.



[1] Hartwig, J. *Organotransition Metal Chemistry: From Bonding to Catalysis*; University Science Books: Sausalito, CA, 2010
[2] Sunliang Cui, Yan Zhang, Qifan Wu, *Chem. Sci.*, **2013**, 4, 3421–3426
[3] Gabriele Fumagalli, Steven Stanton, John F. Bower, *Chem. Rev*., **2017**, 117, 9404-9432
[4] Joséphine Caruano, Guilio Muccioli, Raphaël Robiette *Org. Biomol. Chem.* **2016**, 14, 10134−10156.

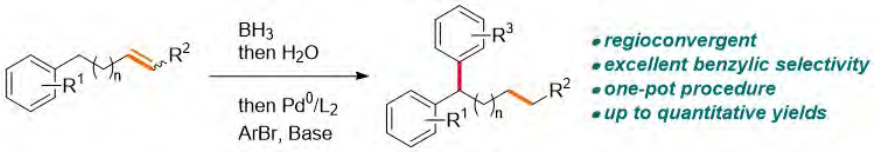
One-Pot Alkene Hydroboration – Palladium Catalyzed Migratory Suzuki – Miyaura C(sp^3) – C(sp^2) Cross-Coupling

Y. Baumgartner[1], O. Baudoin[1]*

[1]Department of Chemistry, University of Basel, St. Johanns-Ring 19, 4056 Basel, Switzerland

The development of C-H bond functionalization has exponentially increased since the start of the 21th century expanding the organic reaction toolbox. Challenging site-selective transformations were e.g. achieved with the introduction of a directing group or by exploiting the intrinsic reactivity of the substrates.[1] An alternative to these extensively researched methods exploits the controlled migration of the organotransition-metal species along an alkyl chain to the cross-coupling site.[2] Our group has been employing this strategy multiple times over the last years for the Pd-catalyzed β- or longer-range arylation of ester enolates, secondary organozinc reagents as well as surrogates.[3]

Here we report the one-pot hydroboration of unactivated internal olefins and migratory Suzuki-Miyaura cross-coupling to the benzylic position.[4] The selectivity is achieved by careful selection of reaction conditions, the o-chlorine substituent on the electrophilic coupling partner and blocking the terminal position.



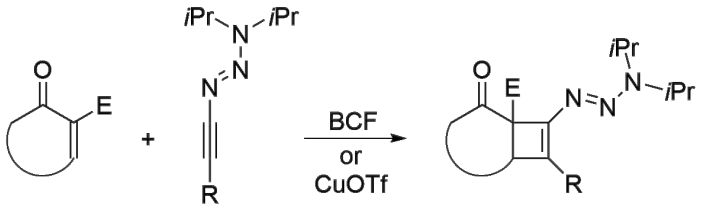
[1] a) J.-Q. Yu, Ed.; *Science of Synthesis; Georg Thieme Verlag KG: Stuttgart-New York* **2015**, Vol. 1−2. b) J. F. Hartwig, *J. Am. Chem. Soc*. **2016**, *138*, 2−24.
[2] a) E. Larionov, H. Li, C. Mazet, *Chem. Commun.* 2014, *50*, 9816-9826; b) A. Vasseur, J. Bruffaerts, I. Marek, *Nat. Chem.* 2016, *8*, 209-219; c) H. Sommer, F. Juliá-Hernández, R. Martin, I. Marek, *ACS Cent. Sci.* 2018, *4*, 153-165; d) T. Kochi, S. Kanno, F. Kakiuchi, *Tetrahedron Lett.* 2019, *60*, 150938.
[3] a) O. Baudoin, *Chimia* **2016**, *70*, 768-772. b) W. Lin, K.-F. Zhang, O. Baudoin, *Nature Catalysis* **2019**, *2*, 882-888.
[4] Y. Baumgartner, O. Baudoin, *submitted manuscript.*

Ficini-Type Reactions with 1-Alkynyltriazenes

C. T. Bormann[1], K. Severin[1]*

[1]École Polytechnique Fédérale de Lausanne (EPFL)

The Ficini reaction represents a straightforward way to synthesize cyclobutenes from N-substituted alkynes and unsaturated ketones. Originally described by Ficini using ynamines[1] its scope was later expanded to ynamides by Hsung[2] and Mezzetti.[3,4] We report the use of 1-alkynyltriazenes for the construction of 1-cyclobutenyltriazenes by a Lewis-acid catalyzed Ficini reaction.



For unsaturated ketones (E = H), the triazene undergoes reaction in the presence of tris(pentafluoro-phenyl)borane (BCF) in toluene. For unsaturated β-ketoesters (E = CO_2R), Cu(OTf) in DCM is a suitable catalytic system. Both reactions proceed at room temperature with good to very good yields and complete regioselectivity. The reactivity of the products is currently under investigation.

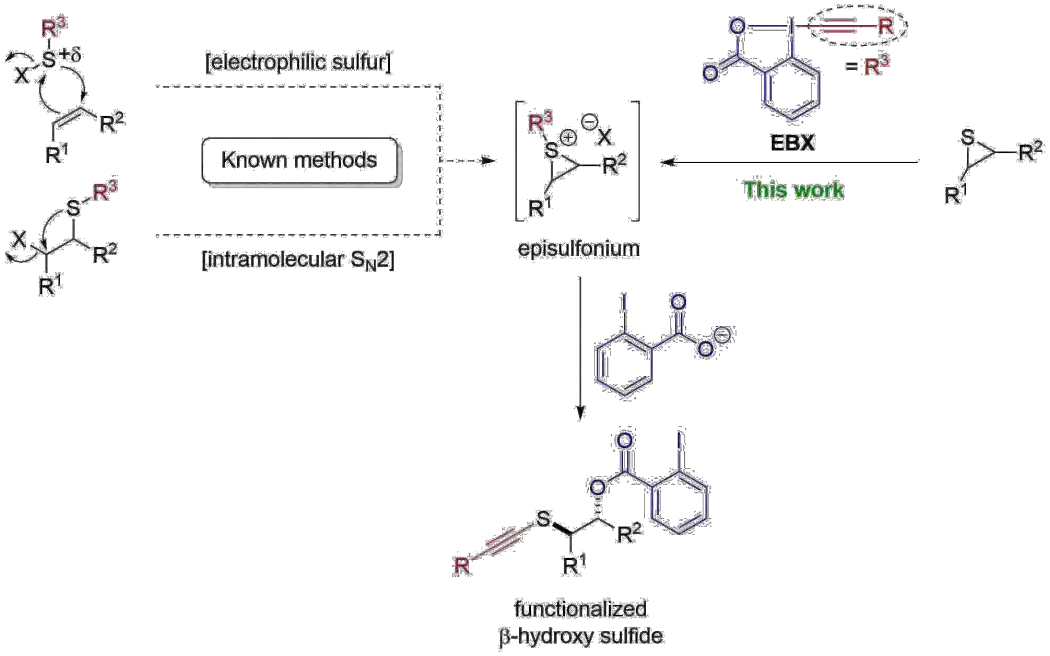
[1] J. Ficini, A. Krief, *Tetrahedron Lett.* **1969**, 10, 1431–1434.
[2] H. Li, R. P. Hsung, K. A. DeKorver, Y. Wei, *Org. Lett.* **2010**, 12, 3780–3783.
[3] C. Schotes, A. Mezzetti, *Angew. Chem. Int. Ed.* **2011**, 50, 3072–3074.
[4] C. Schotes, A. Mezzetti, *J. Org. Chem.* **2011**, 76, 5862–5866.

Synthesis of Functionalized β- and γ-Hydroxy Sulfides by Oxy-Alkynylation of Thiiranes and Thietanes.

J. Borrel[1], G. Pisella[1], J. Waser[1]*

[1]Laboratory of Catalysis and Organic Synthesis (LCSO), Institute of Chemical Sciences and Engineering (ISIC), EPFL

style="text-align: justify;">Episulfoniums are reactive species involved in different types of transformations. They are usually accessed from prefunctionalized thioethers via a S_N2 or by the reaction of alkenes with an electrophilic sulfur source.[1] Their formation by the direct functionalization of thiiranes with an electrophile is mostly unexplored with only a few methodologies utilizing this pathway.[2] Previously, our group reported the electrophilic alkynylation of thiols with ethynylbenziodoxolones (EBX).[3] Using this prior knowledge, we speculated that an alkynylated episulfonium intermediate could be accessed by reacting a thiirane with an EBX reagent. During the process the released carboxylate could act as a nucleophile for a subsequent addition on the intermediate. Herein, we report the ring opening of thiiranes using EBX reagents to access functionalized β-hydroxy sulfides in moderate to good yields.[4] The reaction is copper catalyzed and probably occurs through the formation of a highly reactive alkynyl-episulfonium intermediate. The transformation is tolerant to a vast variety of EBX reagents and thiiranes, the scope could be extended to thietanes to afford γ-hydroxy sulfides. Discussion about this research will be possible during a zoom meeting on Tuesday 25.08.2020, 12:15-13:15.[5]



[1] (a) Song Lin, Eric N. Jacobsen, *Nat. Chem.*, **2012**, 4, 817−824. (b) Scott E. Denmark, Alex Jaunet, *J. Am. Chem. Soc.*, **2013**, 135, 6419−6422.
[2] (a) Christopher M. Rayner, Synthetic Transformations Involving Thiiranium Ion Intermediates. In *Organosulfur Chemistry*; Elsevier, **1995**; Chapter 3, Vol. *1*, pp 89−131. (b) Jun Dong, Hongguang Du, Jiaxi Xu, *J. Org. Chem.*, **2019**, 84, 10724−10739. (c) Przemyslaw Frei, D. Heulyn Jones, Steven T. Kay, Jayde A. McLellan, Blair F. Johnston, Alan R. Kennedy, Nicholas C. O. Tomkinson, *J. Org. Chem.*, **2018**, 83, 1510−1517.
[3] (a) Reto Frei, Jerome Waser, *J. Am. Chem. Soc.*, **2013**, 135, 9620−9623. (b) Reto Frei, Matthew D. Wodrich, Durga Prasad Hari, Pierre-Antoine Borin, Clément Chauvier, Jerome Waser, *J. Am. Chem. Soc.*, **2014**, 136, 16563−16573.
[4] Julien Borrel, Guillaume Pisella, Jerome Waser, *Org. Lett.*, **2020**, 22, 422−427.

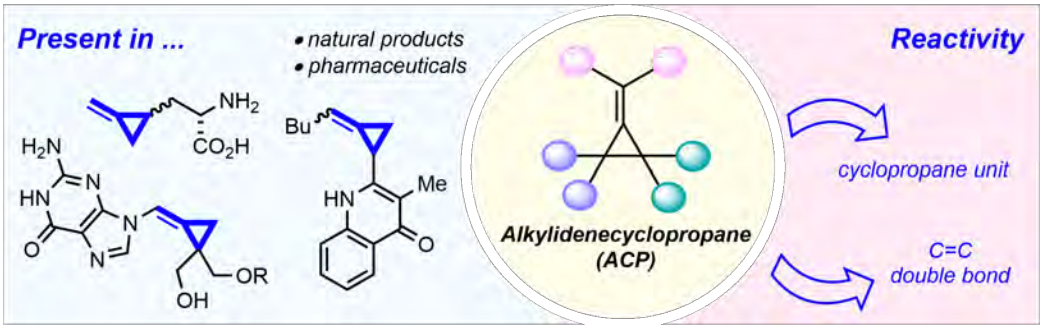
[5] The link will be available on the following document shortly before: https://drive.google.com/file/d/1s1Tg48ABj5q010FyUV29sckTHGopQv6o/view?usp=sharing

A Chiral Naphthyridine Diimine Ligand Platform Enables Nickel-Catalyzed Asymmetric Alkylidenecyclopropanations

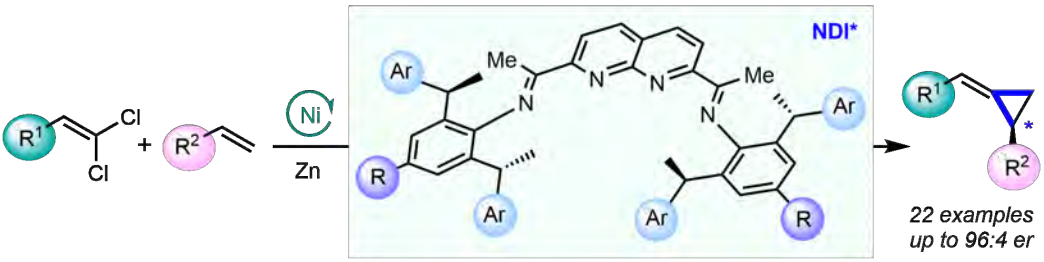
E. Braconi[1], N. Cramer[1]*

[1]EPFL Lausanne, Switzerland

Alkylidenecyclopropanes (ACPs) are members of the cyclopropane family possessing a trigonal carbon center embedded into a three-membered ring.[1] In spite of their high strain, exceeding the one of saturated cyclopropanes by more than 10 kcal/mol, ACPs are surprisingly stable compounds.[2] Alkylidenecyclopropanes have been found in natural products,[3] as well as in pharmaceuticals.[4] In addition, given their high chemical reactivity,[5] ACPs have been shown to engage in a plethora of chemical transformations, involving the cyclopropane unit or the C=C double bond.



A novel class of chiral naphthyridine diimine ligands (NDI*) readily accessible from C_2-symmetric 2,6-di-(1-arylethyl)anilines is described. Their utility, in particular a member with fluorinated aryl side arms, is demonstrated by a reductive Ni-catalyzed enantioselective alkylidene transfer reaction from 1,1-dichloroalkenes to olefins. This transformation provides direct access to a broad range of synthetically valuable alkylidenecyclopropanes in high yields and enantioselectivities.



[1] Richard S. Grainger, Kevin R. Munro, *Tetrahedron* **2015**, 71, 7795-7835.
[2] a) Robert D. Bach, Olga Dmitrenko, *J. Am. Chem. Soc.* **2004**, 126, 4444-4452; b) Kenneth B. Wiberg, Richard A. Fenoglio, *J. Am. Chem. Soc.* **1968**, 90, 3395-3397.
[3] a) J. R. Evans, Eunice J. Napier, R. A. Fletton, *J. Antibiot. (Tokyo)* **1978**, 31, 952-958; b) C. H. Hassall, K. Reyle, P. Feng, *Nature* **1954**, 173, 356-357.
[4] Shaoman Zhou, Julie M. Breitenbach, Katherine Z. Borysko, John C. Drach, Earl R. Kern, Elizabeth Gullen, Yung-Chi Cheng, Jiri Zemlicka, *J. Med. Chem.* **2004**, 47, 566-575.
[5] a) Hélène Pellissier, *Tetrahedron* **2010**, 66, 8341-8375; b) Alberto Brandi, Stefano Cicchi, Franca M. Cordero, Andrea Goti, *Chem. Rev.* **2014**, 114, 7317-7420.

Organocatalyzed Conjugate Addition Reactions of Aldehydes to Nitroolefins with *Anti*-Selectivity

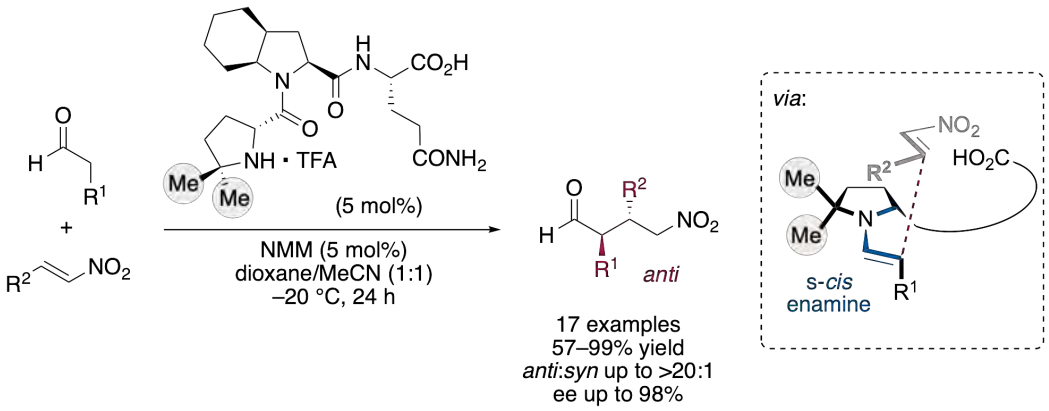
A. Budinská[1], T. Schnitzer[1], H. Wennemers[1]*

[1]Laboratory of Organic Chemistry, D-CHAB, ETH Zürich

In the past two decades, stereoselective conjugate addition reactions of aldehydes to nitroolefins using amine organocatalysts have been a subject of intense research.[1] The resulting products, γ-nitroaldehydes, are versatile synthetic intermediates that can be further derivatized into key moieties present in bioactive compounds such as pyrrolidines and γ-butyrolactams. Yet, the conjugate addition products are typically obtained as *syn*-diastereoisomes.[1] Broadly applicable, non-substrate specific *anti*-selective methods remain unprecedented.

Our group introduced highly reactive tripeptidic catalysts of the type H-Pro-Pro-Xaa (Xaa = any amino acid), which catalyze conjugate addition reactions of carbonyl compounds to nitroolefins in high yields and with excellent *syn*-diastereoselectivity and enantioselectivity.[2] Detailed mechanistic and conformational studies on these tripeptides showed that the s-*trans* enamine intermediate is involved in the rate- and stereoselectivity-determining step.[3]

Drawing on this knowledge and the ease of structural modification of peptides, we envisioned that a general *anti*-selective catalyst could be developed.[4] Key to the reversal of diastereoselectivity are substituents at the Cδ position of the reactive pyrrolidine that favor the C–C bond formation via a s-*cis*-configured enamine. Different aldehydes and nitroolefins were converted to *anti*-configured γ-nitroaldehydes in high yields and stereoselectivities, highlighting the generality of our methodology. NMR spectroscopic and computational insights corroborated the preferential formation of s-*cis* enamine and showed that the catalytic system operates under a Curtin-Hammett scenario.



[1] a) D. A. Alonso, A. Baeza, R. Chinchilla, C. Gómez, G. Guillena, I. M. Pastor, D. J. Ramón, *Molecules* **2017**, *22*, 895–945.
[2] For examples, see: a) M. Wiesner, J. D. Revell, H. Wennemers, *Angew. Chem. Int. Ed.* **2008**, *47*, 1871–1874. b) R. Kastl, H. Wennemers, *Angew. Chem. Int. Ed.* **2013**, *52*, 7228–7232.
[3] a) F. Bächle, J. Duschmalé, C. Ebner, A. Pfaltz, H. Wennemers, *Angew. Chem. Int. Ed.* **2013**, *52*, 12619–12623. b) C. Rigling, J. K. Kisunzu, J. Duschmalé, D. Häussinger, M. Wiesner, M. O. Ebert, H. Wennemers, *J. Am. Chem. Soc.* **2018**, *140*, 10829–10838.
[4] T. Schnitzer, A. Budinská, H. Wennemers, *Nat. Catal.* **2020**, *3*, 143–147.

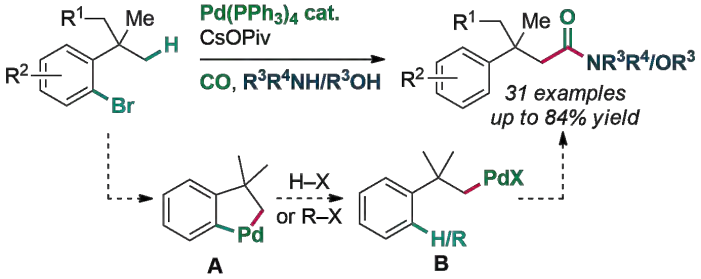
Synthesis of Amides and Esters *via* Pd^0-Catalyzed Carbonylative C(sp^3)-H Activation / 1,4-Pd Shift

T. Čarný[1], R. Rocaboy[1], A. Clemenceau[1], O. Baudoin[1]*

[1]Department of Chemistry, University of Basel, Switzerland

Pd^0-catalyzed activations of C(sp^3)–H bonds have proven a powerful method to construct C–C bonds and produce an array of useful carbo- and heterocycles.[1] Trapping of reaction intermediates, such as palladacycles or σ-alkylpalladium complexes, allows formation of various interesting products. Indanes can be formed by trapping of organopalladacycle **A** with dibromomethane,[2] while indanones are formed upon trapping with CO.[3] The σ-alkylpalladium complex **B** arising from 1,4-Pd shift can either undergo β-H elimination to form olefins,[4] or can be trapped by boronic acids or anilines providing the corresponding arylation or amination products.[5]

We report a method for the synthesis of carboxylic derivatives from aryl bromides, proceeding *via* C(sp^3)–H activation/1,4-Pd shift to give a σ-alkylpalladium intermediate which is further trapped by carbon monoxide and various amines or alcohols.[6] The corresponding amide and ester products bearing a quaternary *β* carbon were isolated up to 84% yield (*Scheme 1*). Mechanistic studies showed that the aminocarbonylation of the σ-alkylpalladium intermediate is fast using PPh_3 as the ligand, and leads to the amide formation rather than the previously reported indanone product.



Scheme 1. Pd^0-catalyzed carbonylative C(sp^3)-H activation / 1,4-Pd shift.

[1] O. Baudoin, *Acc. Chem. Res*. **2017**, *50*, 1114.
[2] Z. Wu, D. Ma, B. Zhou, X. Ji, X. Ma, X. Wang, Y. Zhang, *Angew. Chem. Int. Ed.* **2017**, *56*, 12288.
[3] S.-L. Cai, Y. Li, C. Yang, J. Sheng, X.-S. Wang, *ACS Catal.* **2019**, *9*, 10299.
[4] J. Hitce, P. Retailleau, O. Baudoin, *Chem. Eur. J.* **2007**, *13*, 792; b) E. Motti, M. Catellani, *Adv. Synth. Catal.* **2008**, *350*, 565.
[5] a) T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685; b) J. Pan, M. Su, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2011**, *50*, 8647.
[6] T. Čarný, R. Rocaboy, A. Clemenceau, O. Baudoin, submitted work.

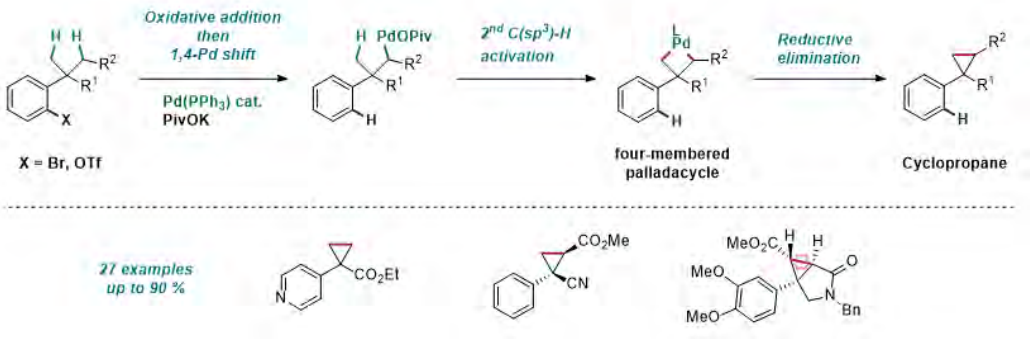
Direct Synthesis of Cyclopropanes from gem-Dialkyl Groups through Double C–H Activation

A. Clemenceau[1,2], P. Thesmar[1], O. Baudoin[1]*

[1]Department of Chemistry, University of Basel, [2]ORIL industries

Palladium-catalyzed C(sp^3)–H functionalisation has been established as a powerful tool to construct various important cyclic systems.[1] To take advantage of this chemistry, we are focusing our efforts on the elaboration of double C(sp^3)-H activation to rapidly access complex natural products[2] and heterocycles.[3]

In this context, we developed an unprecedented synthesis of cyclopropanes, important pharmacophores, via the activation of two alkyl C-H bonds to forge a strained C-C bond. This transformation exploits Pd 1,4-shift,[4] and the isolation of different palladium complex intermediates afforded a valuable insight into the complex mechanistic pathway.[5]



[1] O. Baudoin, *Acc. Chem. Res*. **2017**, *50*, 1114-1123.
[2] P. Thesmar, O. Baudoin, *J. Am. Chem. Soc*. **2019**, *141*, 15779−15783.
[3] R. Rocaboy, I. Anastasiou, O. Baudoin, *Angew. Chem. Int. Ed.* **2019**, *58*, 14625-14628.
[4] J.Q. Yu, Z. Shi, *Top. Curr. Chem.* **2010**, 292, 123
[5] A. Clemenceau, P. Thesmar, M. Gicquel, A. Le Flohic, O. Baudoin, *submitted work.*

Palladium-Catalyzed Di-functionalization of Allylic Amines and Alcohols Using Aldehyde-Derived Tethers

A. K. Das[1], S. Nicolai[1], J. Waser[1]*

[1]Laboratory of Catalysis and Organic Synthesis (LCSO), Institute of Chemical Sciences and Engineering (ISIC), EPFL Lausanne

Alkene di-functionalization through an intermolecular approach presents important challenges of reactivity, regioselectivity and stereoselectivity. The installation of a molecular tether allows addressing the reactivity issue by making the reaction intramolecular. Furthermore, a cyclic transition state facilitates control over regio and stereoselectivity. Our group reported the functionalization of allyl amines and alcohols under Pd catalysis using trifluoroacetaldehyde-derived tethers via amino/oxy-alkynylation and arylation to access amino alcohols[1] or diamines[2] after tether removal. Herein, we will present our recent progress in the area involving different functionalization reactions of alkenes. Discussion about this research will be possible during a zoom meeting on Tuesday 25.08.2020, 12:15-13:15.[3]

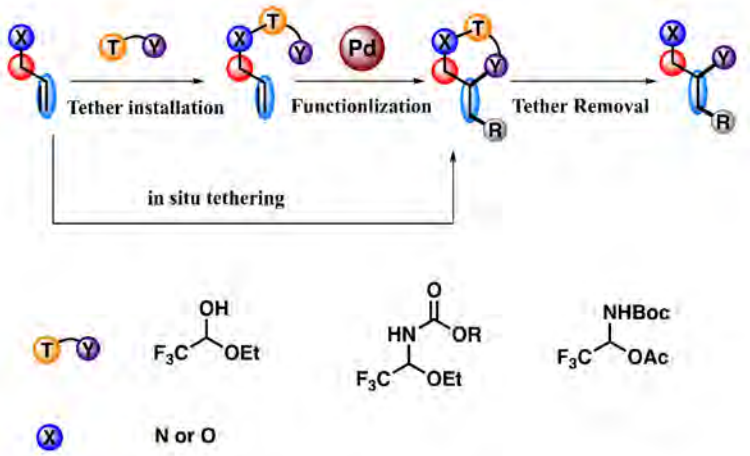


Figure 1. **Palladium-Catalyzed Di-functionalization of Allylic Amines and Alcohols Using Aldehyde-Derived Tethers**

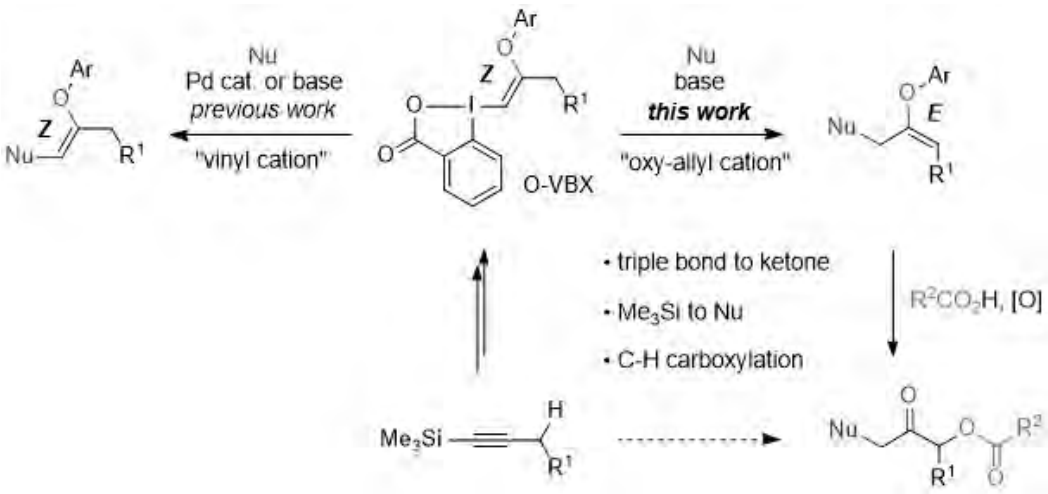
[1] U. Orcel and J. Waser, *Angew. Chem., Int. Ed.*, **2015**, 54, 5250.
[2] U. Orcel and J. Waser, *Angew. Chem., Int. Ed.*, **2016**, 55, 12881.
[3] The link will be available on the following document shortly before: https://drive.google.com/file/d/1s1Tg48ABj5q010FyUV29sckTHGopQv6o/view

Hypervalent Iodine Reagents as Oxy-Allyl Cation Synthetic Equivalents for the Synthesis of Vinyl Ethers and Ketones

N. Declas[1], J. Waser[1]*

[1]Laboratory of Catalysis and Organic Synthesis (LCSO), Institute of Chemical Sciences and Engineering (ISIC), EPFL

Hypervalent iodine reagents are widely used in organic synthesis as efficient group transfer reagents via Umpolung of nucleophiles.[1] Enolates, enol ethers and enamines are among the most important nucleophilic synthons in synthetic chemistry,[2] and the Umpolung of enolates with hypervalent iodine reagents is well established.[3] However, the transformations involve highly reactive intermediates formed *in situ*, and an access to stable reagents is of a high interest. In 2019, our group published a highly stereoselective synthesis of *Z*-enamides and enol ethers based vinylbenziodoxolone reagents (N- and O-VBX), in two steps from silyl alkynes.[4] The enhanced reactivity of the hypervalent bond allowed their use as formal vinyl cations in presence of nucleophiles. Herein we report a new mode of reactivity of O-VBX reagents, acting as oxy-allyl cation synthetic equivalents, a reactivity that differs from the well-established "vinyl-cation" behavior of alkenyl iodonium salts.[5] The new transformation, promoted by an excess of base, is working especially well with phenol nucleophiles, leading to aryl enol ethers bearing an allylic ether with complete *E*-stereoselectivity. In absence of external nucleophiles, the 2-iodobenzoate group of the reagent could be transferred. Under oxidative conditions, the obtained products were transformed in alpha-functionalized ketones, offering a new synthetic pathway to access functionalized ketones from alkynes in three to five steps.[6] Discussion about this research will be possible during a zoom meeting on Tuesday 25.08.2020, 12:15-13h15.[7]



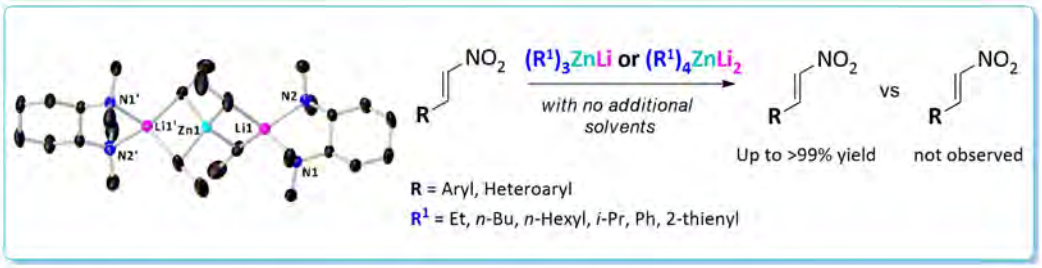
[1] a) V. V. Zhdankin, Hypervalent Iodine Chemistry: Preparation, Structure and Synthetic Applications of Polyvalent Iodine Compounds, In *Hypervalent Iodine Chemistry*; John Wiley & Sons, Ltd, **2013**, pp 1–20; b) A. Yoshimura, V. V. Zhdankin, *Chem. Rev.* **2016**, *116*, 3328. [2] a) G. Stork, J. Szmuszkovicz, R. Terrell, A. Brizzolara, H. Landesman, *J. Am. Chem. Soc.* **1963**, *85*, 207; b) T. Mukaiyama, K. Banno, K. Narasaka, *J. Am. Chem. Soc.* **1974**, *96*, 7503; c) K. Gopalaiah, H. B. Kagan, *Chem. Rev.* **2011**, *111*, 4599. [3] E. A. Merritt, B. Olofsson, *Synthesis* **2011**, 517. [4] P. Caramenti, N. Declas, R. Tessier, M. D. Wodrich, J. Waser, *Chem. Sci.* **2019**, *10*, 3223–3230. [5] T. Okuyama, T. Takino, T. Sueda, M. Ochiai, *J. Am. Chem. Soc.* **1995**, *117*, 3360. [6] N. Declas, J. Waser, *Unpublished results*. [7] The link will be available on the following document shortly
before: https://drive.google.com/file/d/1s1Tg48ABj5q010FyUV29sckTHGopQv6o/view?usp=sharing.

Studying the Effectiveness of Lithium Zincates Species in Michael Addition Reactions: Synthetic and Structural Insights

M. Dell'Aera[1,3], A. Altomare[2], V. Capriati[3]*, E. Hevia[1]*

[1]Department für Chemie und Biochemie, Universität Bern, CH3012, Bern, Switzerland, [2]IC-CNR, Via Amendola 122/o, I-70125, Bari, Italy, [3]Dipartimento di Farmacia-Scienze del Farmaco, Università di Bari, I-70125 Bari, Italy

The conjugate addition of organometallics to nitroalkenes provides a useful method for nitro-alkylation. This type of addition is much pursued in organic synthesis as the nitro group can be easily transformed into various functional groups including carbonyl derivatives by the Nef reaction, amines by reduction, nitriles, imines by other transformations.[1] While 1,4-conjugated additions of organozinc reagents (R_2Zn and RZnX) have been extensively studied,[2] applications of alkali-metal zincates in fundamental organic transformations are still in their infancy.[3] These type of reagents show unique, synergistic chemical characteristics which cannot be replicated by their monometallic (organolithium/organozinc) counterparts. Furthermore, the replacement of the vinylic nitro group by an alkyl group remains a complication encountered when nitrostyrenes are reacted with dialkylzinc compounds in the absence of a Lewis acid.[4] In our recent work we demonstrated that under optimized reaction conditions, 0 °C and with no additional solvents, Michael additions promoted by aliphatic and aromatic organozincates take place with high regio- and chemoselectivity providing the expected nitroalkanes in yields up to >98%, and with no replacement of the vinylic nitro group by the alkyl group.[5]



Based on these findings, the necessity to develop an enantioselective version of this transformation became important. In order to develop an enantioselective reaction, a chiral ligand is known to be necessary. In this case, we thought to create a chiral lithium zincate using two different approaches: harnessing the deprotonative capability of the tetraorganozincate species towards mobile protons like the ones present in amino alcohols and using a co-complexation approach between the corresponding lithium alkoxide of the ligand employed and an organozinc compound. In this communication, isolation of key intermediates as well as structural and synthetic aspects will be discussed.

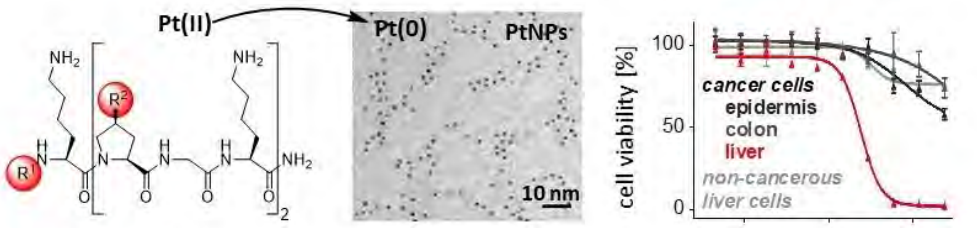
[1] Noboru Ono, The Nitro Group in Organic Synthesis, Wiley-VCH, **2002**
[2] Ben L. Feringa, Mauro Pineschi, Leggy A. Arnold, Rosalinde Imbos, André H. M. de Vries, Angew. Chem. Int. Ed. Engl., **1997**, 36, 2620
[3] David R. Armstrong, Christine Dougan, David V. Graham, Eva Hevia, Alan R. Kennedy, *Organometallics*, **2008**, 27, 6063
[4] Harald Schaefer, Dieter Seebach, *Tetrahedron*, **1995**, 51, 2305-2324
[5] Marzia Dell'Aera, Filippo M. Perna, Paola Vitale, Angela Altomare, Alessandro Palmieri, Lewis C. H. Maddock, Leonie J. Bole, Alan R. Kennedy, Eva Hevia, Vito Capriati, *Chem. Eur. J.* Accepted Author Manuscript. doi:10.1002/chem.202001294

Functionalizable peptide-coated PtNPs for targeting liver cancer cells

E. Engelsberger[1], M. Shoshan[2], H. Wennemers[1]*

[1]Laboratory of Organic Chemistry, D-CHAB, ETH Zürich, [2]University of Zurich

Hepatocellular carcinoma (HCC) is the sixth most frequent cancer and the second leading cause of death from cancer worldwide.[1] FDA approved drugs (e.g. Sorafenib) suffer from low efficacy and severe side effects.[2] Platinum-based drugs – with cisplatin as the most used chemotherapeutic – are very effective but also toxic to healthy organs. Functionalized platinum nanoparticles (PtNPs) are promising alternatives, but previous studies have neither shown improved cytotoxicity nor tumour selectivity of PtNPs over cisplatin.[3,4] Recently our group developed peptide-coated PtNPs that have significantly greater toxicity against hepatic cancer cells (HepG2) than other cancer cells and non-cancerous liver cells, most likely due to the formation of cytotoxic Pt(II) ions under the oxidative conditions in liver cancer cells.[5] The nanoparticle-stabilising peptidic additive H-Lys-[Pro-Gly-Lys]$_2$-NH_2 was discovered through a combinatorial screening of more than 3000 different peptides followed by further optimisation. This peptide enables the formation of water-soluble, monodisperse PtNPs with average diameters of 2.5 nm that are stable for years. Here we present that this heptapeptide can further be used as a platform for the functionalisation of PtNPs. Different functional moieties were attached to the PtNPs for targeting liver cancer cells as well as monitoring or enhancing cellular uptake. The results show the robustness and versatility of the peptide-coated PtNPs.



R = moieties for targeting (e.g. RGD sequence), imaging (e.g. Coumarin derivatives) and/or glucose/galactose derivatives for enhancement of cell uptake

[1] World Cancer Report **2014**, World Health Organization, p. 404.
[2] a) A. Raza, G. K. Sood, *World J. Gastroenterol*. **2014**, *20*, 4115. b) J. M. Llovet, S. Ricci, V. Mazzaferro, J. Bruix, *New Engl. J. Med*. **2008**, *359*, 2508.
[3] H. Mohammadi, A. Abedi, A. Akbarzadeh, M. J. Mokhtari, H. E. Shahmabadi, M. R. Mehrabi, S. Javadian, M. Chiani, *Int. NanoLett*. **2013**, *3*, 28.
[4] P. V. Asharani, N. Xinyi, M. P. Hande, S. Valiyaveettil, *Nanomedicine*, **2010**, *5*, 51.
[5] M. S. Shoshan, T. Vonderach, B. Hattendorf, H. Wennemers, *Angew. Chem. Int. Ed.* **2019**, *58*, 4901–4905.

Through Bond and Space: Curved Light Harvesting Arrays

L. Gallego[1], M. . Rickhaus[1]*

[1]Department of Chemistry, University of Zürich

The properties of flat π-rich molecules have been widely studied and are well known for their use as conductive and optical materials. We know that distorting the systems away from planarity can substantially impact their behaviour, but we know little to what extent. Curved, cyclic, conjugated systems have been lately used in energy transfer processes, with [n]-cycloparaphenylenes and porphyrin nanorings standing out, showing enhanced electronic delocalization and narrower HOMO-LUMO gaps than their linear analogues. Cycloparaphenylenes and derivatives like cycloparaphenylbutadiynylenes (see figure 1, a) have received much attention because of their similarities to carbon nanotubes, while porphyrin-based rings have received attention especially because they mimic arrays of nature's favourite chromophores. Their construction requires evolved tricks to compensate the introduction of strain that comes with macrocyclization.

Here we show our approach towards a nanoring (see figure 1, b) by taking advantage of an inherently curved building block, merging the study of topography with the field of materials science. We chose carpyridine (CP) as monomer, a novel porphyrinoid-related, metal-containg macrocycle bearing two carbazole and two pyridine units alternately connected through ortho aryl-aryl bonds. This arrangement results in a saddle shaped secondary structure. What makes CPs intriguing from a materials perspective is that the carbazoles and the pyridines are decoupled due to the bending. Each monomer by itself has thus limited delocalization. However, when connected through ethynyl bridges to make a nanoring, the conjugation passes from linker via pyridine and goes through the metal, like in a metal doped cycloparaphenylbutadiynylene. The presence of the metal in the CP units also enables hosting a guest by coordination, and when using an acceptor guest, this would allow the study of energy transfer processes from the nanoring through space towards the acceptor.

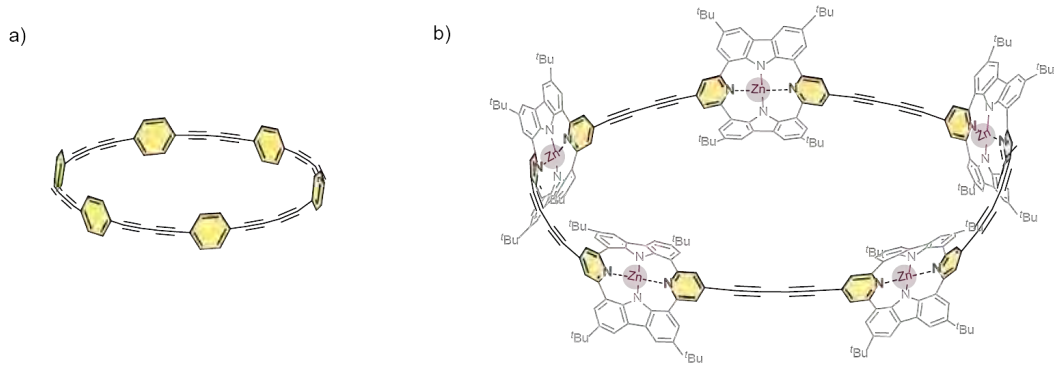


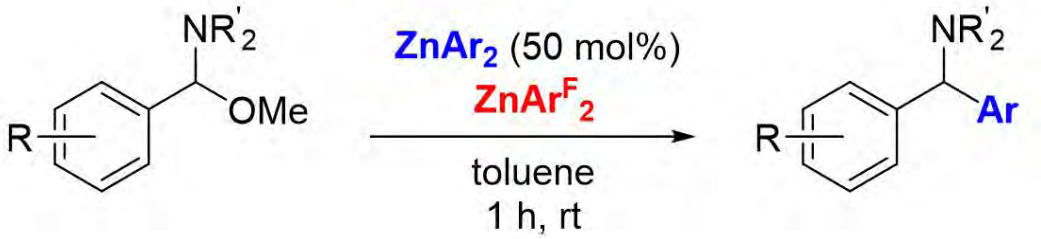
Figure 1: *a) [6]-cycloparaphenylbutadiynylene and b) [5]-cyclocarpyridine*

Transition-Metal-Free Arylation of *N*,*O*-Acetals Using Cooperative Zn/Zn Partnerships

J. M. Gil-Negrete[1], E. Hevia[1]*

[1]Department für Chemie und Biochemie, Universität Bern, CH3012, Bern, Switzerland

Since recent years, the development of more sustainable reaction strategies that represent an alternative to the use of often expensive and toxic transition-metal catalysts has become an important area of research.[1] In this regard, we have recently communicated the arylation of glycosyl bromides based on the synergistic partnership of bis(aryl)zinc reagents with the stronger Lewis acidic [($ZnAr^F_2$)] ($Ar^F = C_6F_5$) in the absence of transition metals and under mild conditions.[2] As part of an ongoing project aimed at expanding this new type of Zn/Zn' synergistic cooperativity, we now report the $ZnAr^F_2$ mediated arylation of *N*,*O*-acetals. The reaction can be carried out using diaryl and heteroaryl zinc reagents with a variety of electron-deficient or electron-rich substrates to afford the corresponding diarylmethanamine products in good yields. The $ZnAr^F_2$ enables the use of a limiting 50 mol% of the diarylzinc reagents, effectively promoting the transference of the two organic groups to the electrophile. Key aspects for the successful outcome of the reaction include avoidance of donor ligands, particularly the use of ethereal solvents such as THF or Et_2O.



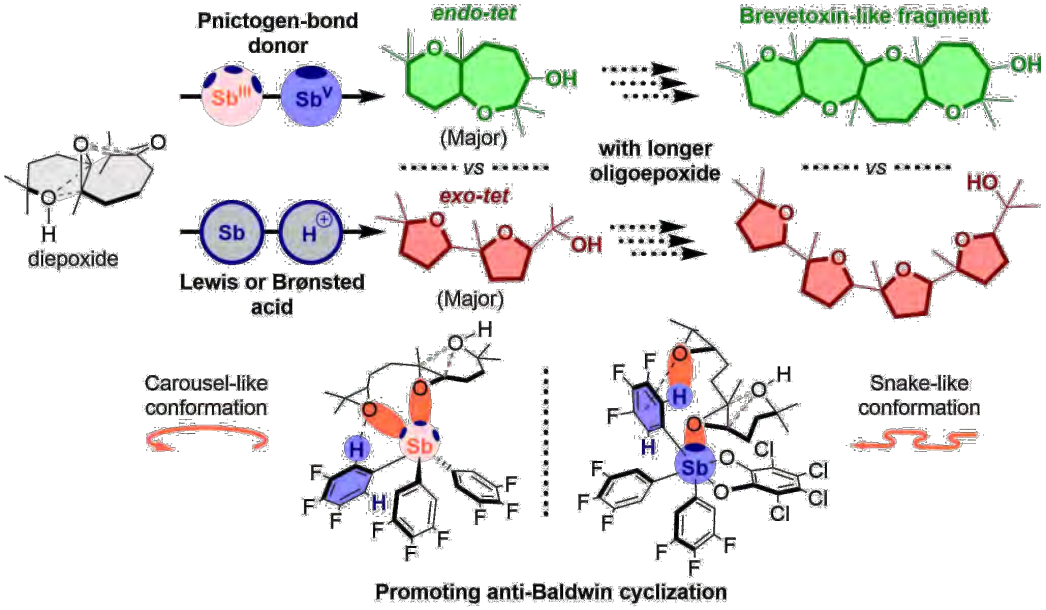
[1] Sun, C.-L.; Shi, Z.-J. *Chem. Rev.* **2014**, *114*, 9219-9280.
[2] Hernán-Gómez, A.; Orr, S. A.; Uzelac, M.; Kennedy, A. R.; Barroso, S.; Jusseau, X.; Lemaire, S.; Farina, V.; Hevia, E. *Angew. Chem. Int. Ed.* **2018**, *57*, 10630-10634.

Pnictogen-Bonding Catalysis: Polyether Cyclizations, Breaking the Baldwin Rules

A. Gini[1], M. Paraja[1], B. Galmés[2], C. Besnard[1], A. I. Poblador-Bahamonde [1], N. Sakai[1], A. Frontera[2], S. Matile[1]*

[1]Department of Organic Chemistry, University of Geneva, [2]Department of Chemistry, University of the Balearic Islands

The long journey into non-covalent interactions is far to be ended. In the last decade the exploitation of halogen-[1] and chalcogen-bond[2] donor as catalyst opened new routes on the application of the so-called σ-hole interactions over more classical non-covalent bond, such as hydrogen bonding. However, the closely related pnictogen- and tetrels-bond interactions are still poorly explored. In this context, pnictogen-bond donors are attractive for use in catalysis because of deep σ-hole, high multivalency, rich hypervalency, and chiral binding pockets.[3]



We here report natural product inspired epoxide-opening polyether cyclizations catalyzed by fluoroarylated Sb(V) > Sb(III) > Bi > Sn > Ge as exotic non-covalent σ-hole donor. The distinctive characteristic found for pnictogen-bonding catalysis is the breaking of the Baldwin rules, that is selective *endo* cyclization into the *trans*-fused ladder oligomers known from the brevetoxins.[4] In addition, tris(3,4,5-trifluorophenyl)stibines and their hypervalent stiborane catecholates afford different anti-Baldwin stereoselectivity, as well as diverse transition-state conformation. Lewis ($SbCl_3$), Brønsted (AcOH) and π acids fail to provide similar access to these forbidden rings.[5] Like hydrogen-bonding catalysis differs from Brønsted acid catalysis, pnictogen-bonding catalysis thus emerges as the supramolecular counterpart of covalent Lewis acid catalysis.

[1] Hui Wang, Weizhou Wang, Wei Jun Jin, *Chem. Rev*. **2016**, 116, 5072-5104.
[2] Lukas Vogel, Patrick Wonner, Stefan M. Huber, *Angew. Chem. Int. Ed.* **2018**, 58, 1880-1891.
[3] Sebastian Benz, Amalia I. Poblador-Bahamonde, Nicolas Low-Ders, Stefan Matile, *Angew. Chem. Int. Ed.* **2018**, 57, 5408-5412.
[4] Ivan Vilotijevic, Timothy F. Jamison, *Angew. Chem. Int. Ed.* **2009**; 48, 5250–5281.
[5] Miguel Paraja, Xiaoyu Hao, Stefan Matile, *Angew. Chem. Int. Ed.* **2020**, 10.1002/anie.202000681

PhotoTags: Photoactivatable fluorophores for protein labelling

A. Guillou[1], J. P. Holland[1]*

[1]University of Zurich, Department of Chemistry, Winterthurerstrasse 190, CH-8057, Zurich

Efficient methods to functionalise proteins are vital in the development of many diagnostic and therapeutic compounds such as radiolabelled monoclonal antibodies (mAbs) for positron emission tomography (PET), fluorescent probes for immunohistochemistry, and antibody-drug conjugates (ADCs). Inherently fluorescent proteins such as green fluorescent protein (GFP) can be used for confocal microscopy, but labelling non-fluorescent proteins extrinsically with organic fluorophores gives access to optical probes with a wider range of biological applications.[1-2] Small-molecule fluorophores derived from the fluorescein, rhodamine, coumarin or BODIPY families are often used for tagging protein. Standard protein-conjugation chemistries for attaching the fluorophore include functionalisation of lysine residues via amide bond formation with activated esters (N-hydroxysuccinimide [NHS]-type chemistry) or the formation of thiourea linkages using fluorophores bearing benzyl-isothiocyanate (Bn-NCS) groups.[3-4]

Recently, our group has been exploring the use of light-induced synthesis of protein-conjugates.[5-6] Here, we present the synthesis and experimental characterisation of four photoactivatable fluorophores (PhotoTags) bearing light-sensitive aryl azide (ArN_3) groups coupled to the fluorophore *via* a water-solubilising *tris*-polyethylene glycol (PEG_3) linker. Photochemical kinetic studies revealed that rapid activation occurs under irradiation at 365 or 395 nm. Irradiation for <10 min at pH8 in the presence of various proteins, including human serum albumin and IgG_1 immunoglobulins, followed by preparative size-exclusion chromatography produced a series of fluorescent protein-conjugates that were characterised further by electronic absorption and fluorescence emission spectroscopy, photobleaching studies, gel electrophoresis, and size-exclusion HPLC. Further experiments are underway to optimise the conditions required for efficient photoactivated protein-functionalisation. A tool-box of different PhotoTags is now available to make fluorescently-tagged proteins literally 'in a flash'.

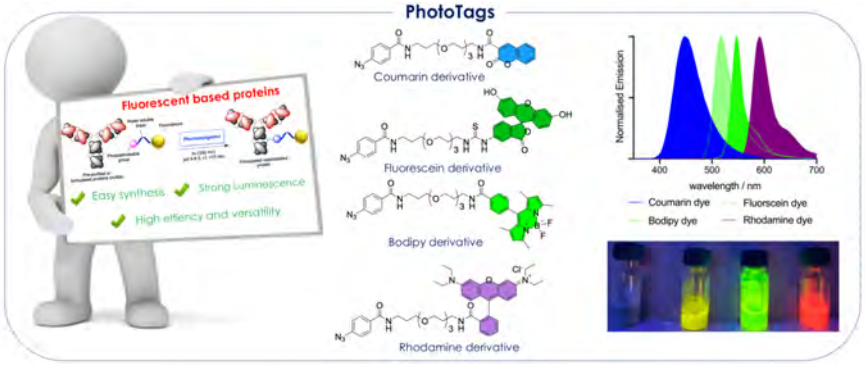


Figure 1. Chemical structures of four classes of photoactivatable dyes (PhotoTags), as well as their (colour-coded) emission spectra, and a photography showing fluorescence under UV irradiation.

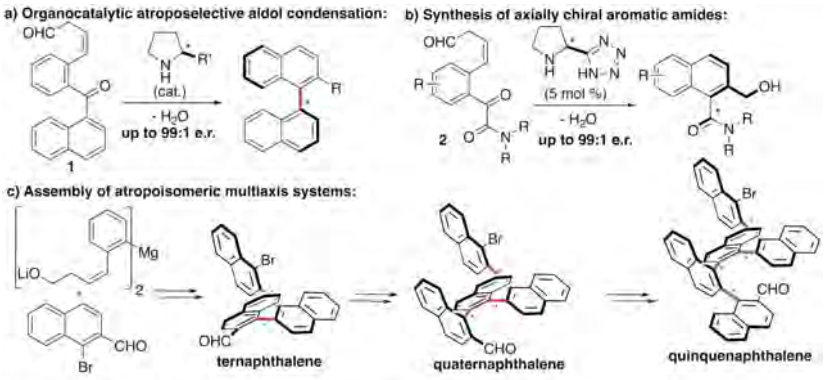
[1] Crivat, G. *et al. Trends Biotechnol.* **2012**, 30, 8−16.
[2] Fujiki, Y. *et al. Cytometry, Part A* **2008**, 73 (2), 11.
[3] Kowada, T. *et al. Chem. Soc. Rev*. **2015**, 44, 4953−4972.
[4] Suzuki, T. *et al. Acta Histochem. Cytochem.* **2007**, 40, 131−139
[5] Fay, R. *et al. Org. Lett.* **2020**, 22, 3499−3503
[6] Guillou, A. et al. *Chem. Eur. J.* 2020 (in press), DOI: 10.1002/chem.202001987

Stereoselective Synthesis of Atropoisomeric Biaryls

Z. Jončev[1], C. Sparr[1]*

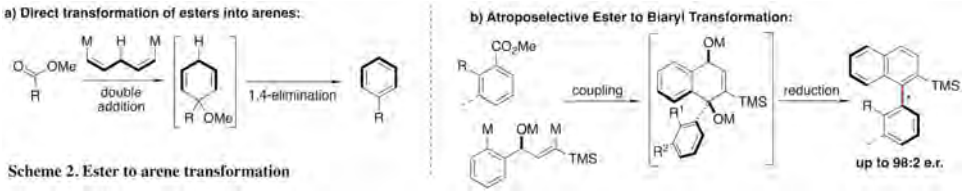
[1]University of Basel

Atropisomers are stereoisomers that arise from the restricted rotation about a single bond. Applications across different disciplines have made these compounds indispensable, therefore different stereoselective methods to construct axially chiral biaryls have been developed. Often, catalyst-controlled atroposelective arene-construction requires transition metals that can be toxic in pharmaceutical ingredients, even in trace amounts. Inspired by the biosynthesis of aromatic polyketides, our group is focusing on the organocatalytic atroposelective aldol condensation. *De novo* construction of arenes that simultaneously leads to a rotationally restricted bond in a stereocontrolled fashion, has been developed to transform unsaturated ketoaldehydes (**1**) or α-ketoamide substrate (**2**) to rotationally restricted compounds with high atroposelectivities and yields (Scheme 1a and 1b). [1,2] Further development of atropodiastereoselective reactions was accomplished by iterative assembly, resulting in remarkable compounds with more than one configurationally stable axis (Scheme 1c). [3]



Scheme 1. Atroposelective arene-forming aldol condensation

Direct ester into arene transformation (dEAT) strategy was developed in our lab using 1,5-bifunctional organomagnesium reagent (Scheme 2a)[4]. Building upon dEAT, atroposelective version allowed for central-to-axial chirality conversion (Scheme 2b).[5] These versatile synthetic concepts provide new reliable methods for the synthesis of various rotationally restricted compounds. The aldol condensation as well as the dEAT are conducted under mild conditions that allow for the preparation of a broad range of functionally distinct atropisomers. Ongoing studies focus on the application of precisely defined molecular frameworks and advancement of new catalytic methods.



Scheme 2. Ester to arene transformation

[1] A. Link, C. Sparr, *Angew. Chem. Int. Ed.* **2014**, *53*, 5458–5461.
[2] V. C. Fäseke, C. Sparr, *Angew. Chem. Int. Ed.* **2016**, *55*, 7261–7264.
[3] D. Lotter, M. Neuburger, M. Rickhaus, D. Häusinger, C. Sparr, *Angew. Chem. Int. Ed.* **2016**, *55*, 2920.
[4] A. Link, C. Fischer, C. Sparr, *Angew. Chem. Int. Ed.* **2015**, *54*, 12163–12166.
[5] A. Link, C. Sparr, *Angew. Chem. Int. Ed.* **2018**, *57*, 7136–7139.

Switching of Chromophores in Optical Antennas

L. Jucker[1], M. Ochs[2], R. Kullock[2], M. Mayor[1,3]*, B. Hecht[2]*

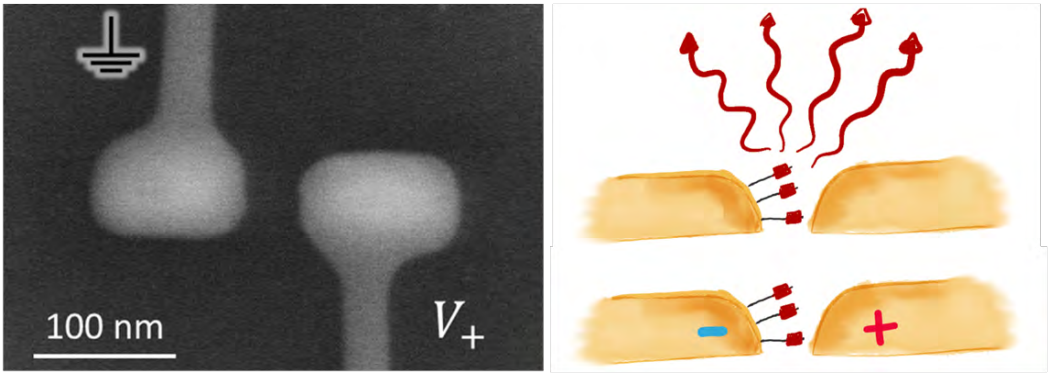
[1]University of Basel, Department of Chemistry, [2]University of Würzburg, Experimental Physics 5, [3] Karlsruhe Institute of Technology, Institute of Nanotechnology

The reversible switching of optical gold antennas by the incorporation of chromophores in the antenna feedgap is presented. Through application of an electric potential difference, we envision a change in photoluminescence intensity, resulting in a simple nanoscale switch.

The gold nanostructures[1] are fabricated by focused ion beam milling of single-crystalline gold flakes placed on a gold electrode, enabling fine-tuning of the antenna to adjust its gap size and optical properties.

The emission wavelength of the synthesized push-pull chromophore overlaps with the surface plasmon resonance of the antenna, increasing the photoluminescence intensity. Incorporation of a thiol-terminated PEG-chain linker ensures self-assembled monolayer formation and sufficient distance of the chromophore to the gold surface to prevent undesired excited state quenching.

The directionality required for switching experiments is obtained through selective voltammetric removal of the self-assembled monolayer from one antenna arm. First measurements examining the behavior of the chromophore in the gold antenna feedgap show reversible switching of the emission intensity upon application of an electric potential difference to the electrodes. Further investigations into the underlying mechanism are ongoing.



[1] Jord C. Prangsma, Johannes Kern, Alexander G. Knapp, Swen Grossmann, Monika Emmerling, Martin Kamp, Bert Hecht, *Nano Letters*, **2012**, 8, 3915-3919.

New Neo-Clerodane Diterpenes from *Teucrium polium*

M. Keller[1], S. Chabane[2], A. Boudjelal[3], M. Hamburger[1], O. Potterat[1]*

[1]Division of Pharmaceutical Biology, University of Basel, Switzerland, [2]Department of Life and Nature Science, Faculty of Sciences, Mohamed Boudiaf University, M'Sila, Algeria, [3]Department of Microbiology and Biochemistry, Faculty of Sciences, Mohamed Boudiaf University, M'Sila, Algeria

The aerial parts of *Teucrium polium* L., popularly known as felty germander, are used in Algerian traditional medicine for the treatment of diabetes, hypertension, and in the form of a powder mixed with petroleum jelly or beeswax as a wound healing agent [1]. The wound healing properties of a methanolic extract was confirmed using a wound excision model in rabbits, and the polyphenolic constituents characterized by HPLC-PDA-MS analysis followed by targeted isolation [2].

For the analysis of the non-phenolic compounds, the ethyl acetate-soluble fraction of the active methanolic extract was separated by preparative HPLC-MS on an RP-18 column. Five neo-clerodane diterpenes were obtained, including the known 20-acetylauropolin and four new congeners. Their structures were elucidated with the aid of extensive NMR analysis and HRESIMS, and ECD. The absolute configuration of 20-acetylauropolin was confirmed by X-ray crystallographic diffraction analysis.

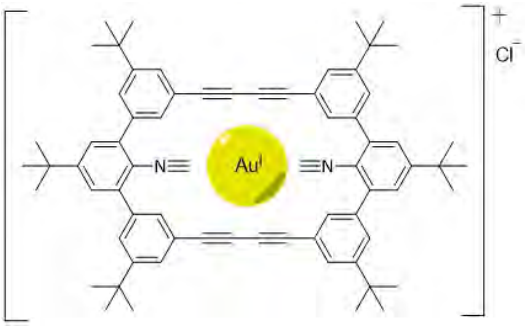
[1] Amel Boudjelal, Cherifa Henchiri, Madani Sari, et al., *Journal of Ethnopharmacology*, **2013**, 148, 395–402.
[2] Sarra Chabane, Amel Boudjelal, Morris Keller, et al., *South African Journal of Botany*, submitted.

Synthesis of a Macrocyclic Gold Atom Acceptor

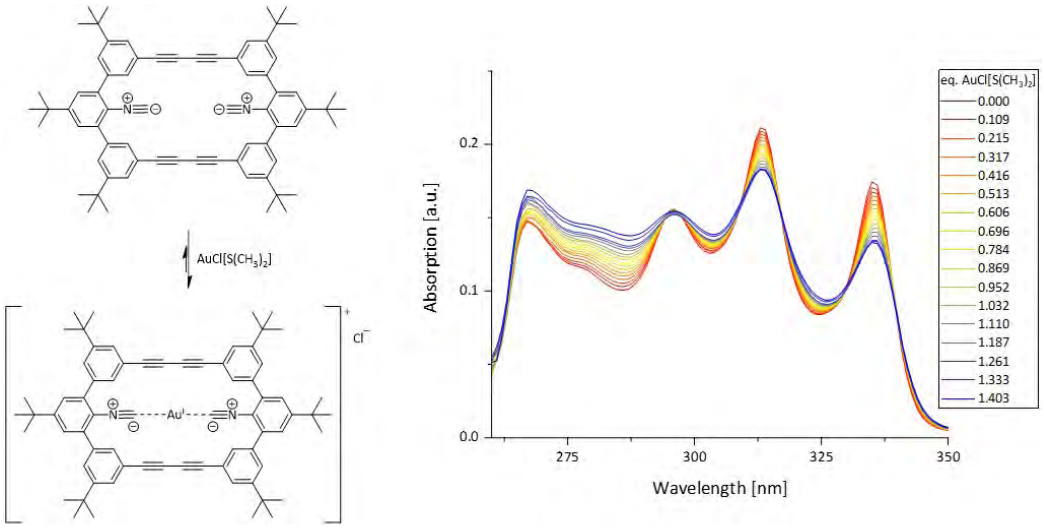
C. Kress[1], P. Zwick[1], M. Mayor[1]*

[1]University of Basel, Department of Chemistry

Isocyanides are suggested to be promising anchoring groups for single molecular junctions measured between gold electrodes.[1,2] This hypothesis was further confirmed by M. Calame *et al.* observing single molecular junction formation of 99% using 1,4-benzenediisocyanide in a liquid environment. Further displacement of the mechanically controlled break junction (MCBJ) resulted in the formation of a one-dimensional coordination polymer, suggesting the release of single gold atoms from the electrode.[3] These findings motivated us to further investigate the isocyanide-gold interaction by studying the affinity of a macrocyclic diisocyanide ligand to gold(I).



The meta-terphenyl macrocycle bearing two isocyanides on opposite sides bridged by butadiynes as spacing groups was designed as a rigid bidentate ligand. The synthesis of this macrocyclic structure was successfully achieved over 7 steps and an overall yield of 7%. The association constant of Au(I) to the macrocycle was determined by UV-vis titration experiments.



[1] Kiguchi, S. Miura, K. Hara, M. Sawamura, K. Murakoshi, *Appl. Phys. Lett.*, **2006**, 89, 213104.
[2] Lörtscher, C. J. Cho, M. Mayor, M. Tschudy, C. Rettner, H. Riel, *ChemPhysChem*, **2011**, 12, 1677–1682.
[3] Vladyka, M. L. Perrin, J. Overbeck, R. R. Ferradás, V. García-Suárez, M. Gantenbein, J. Brunner, M. Mayor, J. Ferrer, M. Calame, *Nat Commun*, **2019**, 10, 1–9.

Brønsted and Lewis acid adducts of triazenes

I. R. Landman[1], A. A. Suleymanov[1], K. Severin[1]*

[1]LCS, ISIC, Ecole Polytechnique Fédérale de Lausanne (EPFL), 1015 Lausanne, Switzerland

The synthetic utility of triazenes rests on the fact that the triazene function can be cleaved by Brønsted or Lewis acids, liberating diazonium compounds. However, the preferred coordination site of the acid is still a matter of debate. We have analyzed triflic acid, $B(C_6F_5)_3$, and $PdCl_2$ adducts of triazenes by NMR spectroscopy and single crystal X-ray crystallography. In all cases, we observe coordination of the acid to the N1 atom of the triazene. This finding is not only of relevance for acid-induced cleavage reactions, but also for metal-catalyzed reactions with triazenes, which are increasingly being used in synthetic organic chemistry.

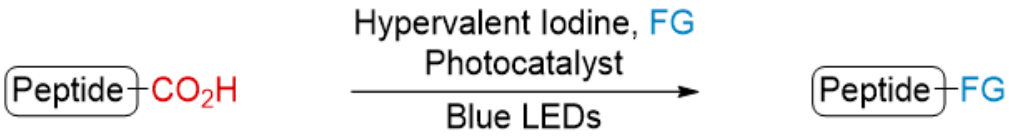
[1] Landman, I. R.; Suleymanov, A. A.; Scopelliti, R.; Fadaei-Tirani, F.; Chadwick, F. M.; Severin, K. *Dalt. Trans.* **2020**, *49*, 2317–2322.

C-Terminal Oxidative Decarboxylative Functionalization of Peptides: a Toolbox Towards Structural Diversity

E. Le Du[1], M. Garreau[1], J. Waser[1]*

[1]Laboratory of Catalysis and Organic Synthesis (LCSO), Institute of Chemical Sciences and Engineering (ISIC), EPFL

Due to the rising interest of peptides in drug discovery, selective chemical peptide modification has emerged as a useful tool.[1] For instance, macrocyclization and bioconjugation of peptides allow to improve their biological properties.[2] Most methods rely on the specific reactivity of the functional groups on the side chains such as thiol (cysteine) or amine (Lysine).[3] However examples of functionalization of the C-terminal position of native peptides are scarce.[4] In this regard, our group recently reported the photocatalyzed oxidative decarboxylative alkynylation of amino acids and peptides.[5] Herein, we present a general platform for the C-terminal functionalization of native peptides. Discussion about this research will be possible during a zoom meeting on Tuesday 25.08.2020, 12:15-13h15.[6]



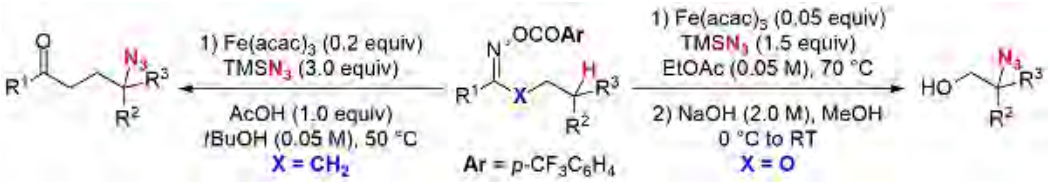
[1] Boutureira, O.; Bernardes, G. J. L. *Chem. Rev.* **2015**, 115, 2174–2195.
[2] Hu, Q.-Y.; Berti, F.; Adamo, R. *Chem. Soc. Rev.* **2016**, 45, 1691–1719.
[3] Sletten, E. M.; Bertozzi, C. R. *Angew. Chem. Int. Ed.* **2009**, 48, 6974–6998.
[4] Malins, L. R. *Pept. Sci.* **2018**, 110, e24049.
[5] (a) Le Vaillant, F.; Courant, T.; Waser, J. *Angew. Chem. Int. Ed.* **2015**, 54, 11200–11204. (b) Garreau, M.; Le Vaillant, F.; Waser, J. *Angew. Chem. Int. Ed.* **2019**, 58, 8182–8186.
[6] The link will be available on the following document shortly before: https://drive.google.com/file/d/1s1Tg48ABj5q010FyUV29sckTHGopQv6o/view?usp=sharing

Iron-catalysed Remote C(sp^3)-H Azidation of *O*-acyl Oximes and *N*-acyloxy Imidates

A. Leclair[1], R. O. Torres-Ochoa[1], Q. Nguyen[1], J. Zhu[1]*

[1]Laboratory of Synthesis and Natural Products, Institut of Chemical Sciences and Engineering, EPFL

Azides are important and versatile building blocks in synthesis, allowing a fast access to an array of different functionalities [1] (e.g. amines, triazoles), notably highlighted by their use in bioconjugation[2][3]. Under the action of a catalytic amount of iron(III) acetylacetonate [$Fe(acac)_3$], various ketoxime esters and *N*-acyloxy imidates were reacted with trimethylsilyl azide ($TMSN_3$) achieving a new access to *γ*-azido ketones and *β*-azido alcohols[4].



This novel remote C(sp^3)-H bond azidation occurred following a sequence of reductive generation of iminyl or imidate radical, 1,5-hydrogen atom transfer (1,5-HAT) and iron-mediated redox azido transfer to the translocated carbon radical. In this unprecedented transformation, the iron catalyst does not only act as a reductant for the generation of the key radical intermediates but also as a platform to promote the redox transfer of the azido moiety. This methodology was successfully applied to the synthesis of a broad variety of *γ*-azido ketones and *β*-azido alcohols in moderate to excellent yield.

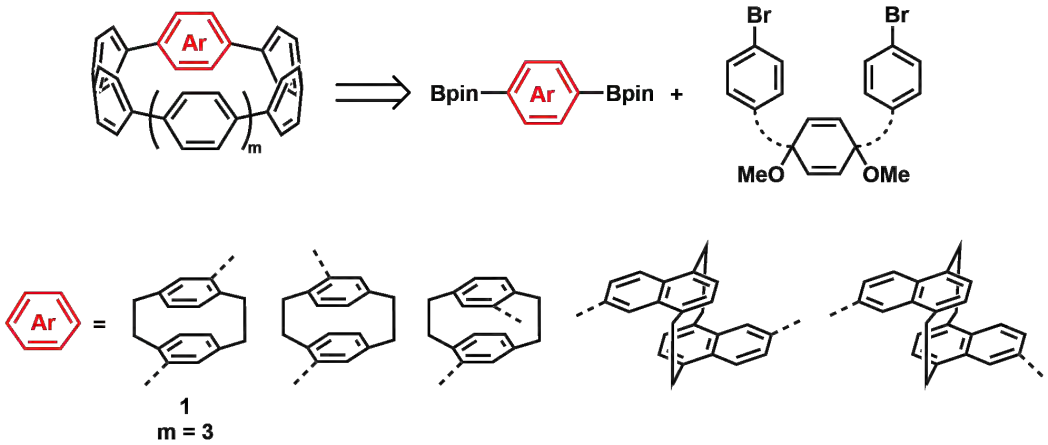
[1] Stefan Bräse, Carmen Gil, Kerstin Knepper, Viktor Zimmermann, *Angew. Chem. Int. Ed.* **2005**, 44, 5188-5240.
[2] Qian Wang, Timothy R. Chan, Robert Hilgraf, Valery V. Fokin, K. Barry Sharpless, M. G. Finn, *J. Am. Chem. Soc.* **2003**, 125, 3192-3193.
[3] Christine I. Schilling, Nicole Jung, Moritz Biskup, Ute Schepers, Stefan Bräse,*Chem. Soc. Rev.* **2011**, 40, 4840-4871.
[4] Rubén Omar Torres-Ochoa, Alexandre Leclair, Qian Wang, Jieping Zhu, *Chem. Eur. J.* **2019**, 25, 9477-9484.

[2^n]Cyclophane carbon nanohoops

J. Malinčík[1], K. Reznikova[1], T. Šolomek[1]*

[1]Department of Chemistry, University of Basel

The lack of synthetic control over the chirality of curved carbon nanostructures derived from graphene, such as carbon nanotubes (CNTs), prevents the development of molecular electronics applications that require high purity and uniformity of these materials. Single- and multi-walled CNTs are typically formed as a mixture of chiral, armchair and zigzag nanostructures that significantly differ in their properties. [1] The urgency of controlled chirality-specific synthesis of CNTs advanced the synthesis of curved molecular nanocarbons – molecular precursors for a stepwise synthesis of uniform single-walled CNTs. Applications in bioimaging, sensing, catalysis and organic electronics have been rapidly emerging on account of the unusual properties of these hoop-like molecular nanocarbons. [2] Analogous molecular precursors for topologically more complex carbon nanostructures are scarce because their topologies do not have a stable molecular representation. For instance, single-walled CNTs can be considered as a rolled up sheet of graphene with connected edges but graphene can be rolled further into a carbon nanoscroll with free edges. Such a structure holds together thanks to a collective action of van der Waals forces that overcome energetically unfavorable bending of the sp^2-hydridized aromatic systems. [3]
In this work, we designed a series of molecular nanoscrolls based on a previously reported molecular fragment **1** [4], where the spiral topology is clipped with the help of a cyclophane unit (Figure 1) to compensate the insufficient van der Waals forces in these molecular nanoscrolls. We utilize [2.2]paracyclophane and [2.2](1,4)-naphthalenophane moieties as such covalent tethers. We investigate the effect of cyclophane substitution pattern on the spiral shape, and its size and the number of phenylene units (*m* in Figure 1) on photophysical properties of these molecular nanoscrolls to establish a clear structure-property relationships.



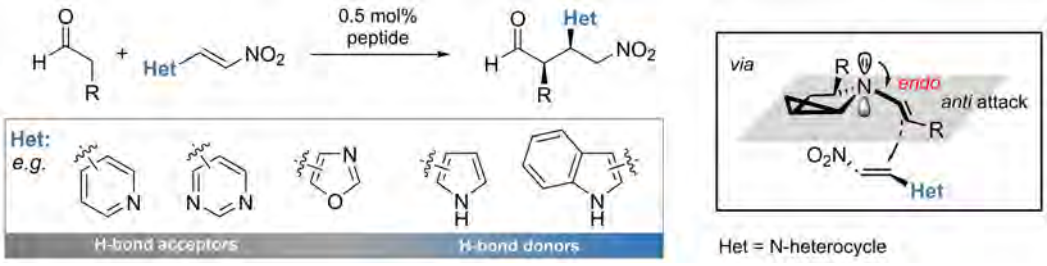
[1] P. M. Ajayan, *Chem. Rev.*, **1999**, 99, 1787.
[2] Erik J. Leonhardt, and Ramesh Jasti, *Nat. Rev. Chem.*, **2019**, 3, 672.
[3] Zhigang Liu, Junfeng Gao, Gang Zhang, Yuan Cheng, and Yong-Wei Zhang,*Nanotechnology*, **2017**, 38, 385704.
[4] Yayu Wu, Guilin Zhuang, Shengsheng Cui, Yu Zhou, Jinyi Wang, Qiang Huang, and Pingwu Du, *Chem. Commun.*, **2019**, 55, 14617.

A Conformationally Tailored Peptide Catalyst Allows for Amine Catalysis with N-Heterocyclic Moieties

J. S. Möhler[1], T. Schnitzer[1], H. Wennemers[1]*

[1]Laboratory of Organic Chemistry, D-CHAB, ETH Zürich

Proline and related α-substituted chiral amines are powerful catalysts for stereoselective C–C bond forming reactions that proceed *via* an enamine intermediate.[1] The conjugate addition reaction between aldehydes and nitroolefins, as a prominent example, provides synthetically versatile γ-nitroaldehydes that allow for straightforward transformations into *e.g.* 3,4-disubstituted pyrrolidines and γ-butyrolactams. These are common motifs in bioactive compounds, especially, if substituted with N-heterocyclic moieties.[2] For organocatalytic transformations, however, unprotected N-heterocyclic moieties can pose a major challenge due to undesired interactions with the catalyst or reaction intermediates *via e.g.* competitive hydrogen bonding. Hence, catalysts need to be sufficiently robust and stereoselective to enable the desired transformation, ideally at low catalyst loadings. Our group has developed peptides of the type H-Pro-Pro-Xaa as highly reactive and stereoselective catalysts for C−C bond formations.[3] Recently, we showed that the reactivity of α-substituted pyrrolidines can be increased by defining the pyramidalization of the enamine-nitrogen.[4] This finding allowed for the first time for organocatalytic conjugate addition reactions of aldehydes with a broad range of nitroolefins bearing N-heterocyclic moieties. The γ-nitroaldehydes were obtained in excellent yields and stereoselectivities using as little as 0.5 mol% of the carefully tailored peptidic catalyst.[5] We also show that the formation of an *endo* -pyramidalized enamine-nitrogen is key for the high stereoselectivity and thereby provide general guidelines for the optimization of chiral 2° amines that catalyze reactions *via* an enamine-based mechanism.



[1] a) Santanu Mukherjee, Jung W. Yang, Sebastian Hoffmann, Benjamin List, *Chemical Reviews,* **2007**, 107, 5471–5569; b) You Q. Zou, Fabian M. Hörmann, Thorsten Bach, *Chemical Society Reviews,* **2018**, 47, 278–290.
[2] Edon Vitaku, David T. Smith, Jon T. Njardarson, *Journal of Medicinal Chemistry,* **2014**, 57, 10257–10274.
[3] For examples see: a) Philipp Krattiger, Roman Kovasy, Jefferson D. Revell, Stanislav Ivan, Helma Wennemers, *Organic Letters,* **2005**, 7, 1101–1103; b) Markus Wiesner, Jefferson D. Revell, Helma Wennemers, *Angewandte Chemie - International Edition,* **2008**, 47, 1871–187; c) Claudio E. Grünenfelder, Jessica K. Kisunzu, Helma Wennemers, *Angewandte Chemie - International Edition,* **2016**, 55, 8571–857; d) Tobias Schnitzer, Alena Budinská, Helma Wennemers, *Nature Catalysis,* **2020**, 3, 143–147.
[4] Tobias Schnitzer,‡ Jasper S. Möhler,‡ Helma Wennemers, *Chemical Science*, **2020**, 11, 1943–1947.
[5] Jasper S. Möhler,‡ Tobias Schnitzer,‡ Helma Wennemers, *manuscript submitted*.

At the Core of Dynamic Polymers: The Self-Assembly of Twisted Aryl Amines

M. Nehme[1], M. Rickhaus[1]*

[1]University of Zürich, Department of Chemistry

Conventionally, chemistry relies on the covalent bond for the construction of molecular systems. While highly versatile for small systems, this strategy is less suited to build large architectures (> 1 nm). The possibility to create interfaces between the versatile world of tailored molecules and real-world devices necessitates a better understanding of objects that span many nanometers. Thus, the mastering of non-covalent interactions becomes essential. Using those, one can guide small, cheap and customizable building blocks to spontaneously arrange themselves into arrays of higher order, bridging the size gap. Supramolecular polymers are arrays, whose monomeric units are held together by unidirectional and reversible noncovalent interactions. The simplest representation of a supramolecular polymer is the columnar stack, where discotic monomers containing flexible side chains and a planar core form unidimensional assemblies. One such model are substituted N-triphenylamines (TPA) that can form helical structures via tri-intermolecular H-bonds. To date, there is no reliable method to predict how exactly a given building block will organize itself in solution or the solid state, consequently allowing us to formulate the following questions:

1. What rules govern supramolecular order? And how do we encode these rules into molecular building blocks?

2. Can we predict new properties that emerge as a result of an assembly of subunits?

To address these seminal goals, we aim to study the influence of systematic variations of the core of a triarylamine trisamide (TATA) core unit, while keeping the outer layer (i.e. sidechains) constant. This ensures that the main driving force for the assembly (the hydrogen bonds) located at the periphery remain in place, leading to columnar stacking. For this purpose, we have devised Family A, which aims at highlighting different parameters such as geometry, steric hindrance, size, and flexibility. Family A (Figure 1) will be dedicated to a series of TATA derivatives with distorted cores. Besides the TPA core, these systems feature a secondary alkyl linkage of different length (C0C3) that connects each aryl with its neighbor. The length of the bridge is anticipated to induce different degrees of twist to the core, distorting the available π-surface. The main objective in this family is thus to investigate if it is possible to find a direct relationship between the distortionof the flat surface and the observed degrees of supramolecular order.

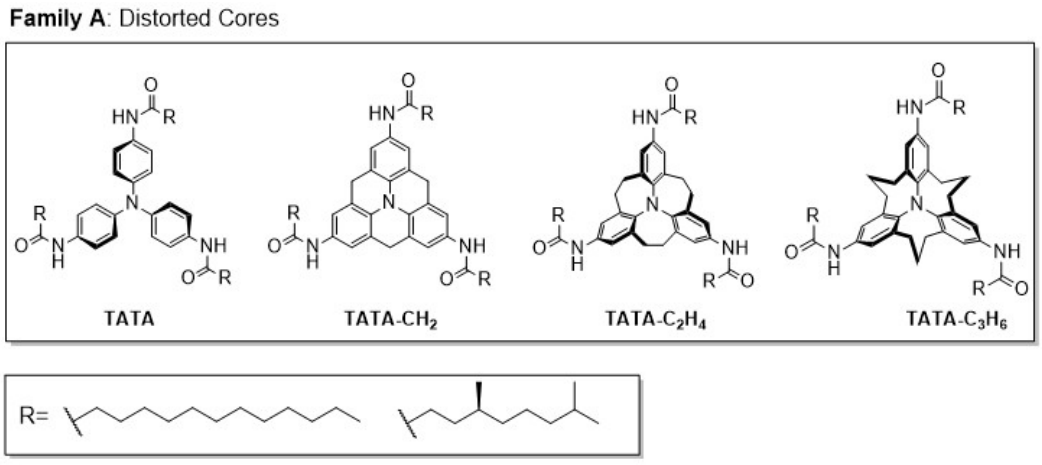


Figure 1. The molecular structures of the desired compounds

Intermolecular Palladium(0)-Catalyzed Atropo-enantioselective C-H Arylation of Hereroarenes

Q. Nguyen[1,2]

[1]Laboratory of Asymmetric Catalysis and Synthesis, [2]EPFL Lausanne

Atropisomeric (hetero)biaryls are motifs with increasing significance in ligands, natural products and biologically active molecules. The straightforward construction of the stereogenic axis by efficient C–H functionalization methods is extremely rare and challenging. An intermolecular and highly enantioselective C–H arylation of relevant heteroarenes providing an efficient access to atropisomeric (hetero)biaryls is reported. The use of a Pd(0) complex equipped with H_8-BINAPO as chiral ligand enables the direct functionalization of a broad range of 1,2,3-triazoles and pyrazoles in excellent yields and selectivities of up to 97.5:2.5 *er*. The method also allows for an atroposelective double C–H arylation for the construction of two stereogenic axes with >99.5:0.5 *er*.

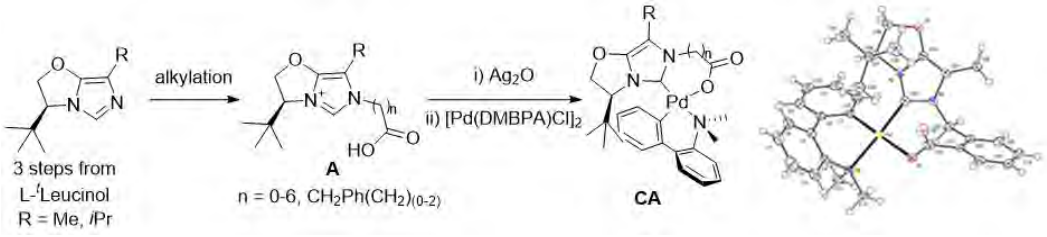
[1] For a review, see Shi, B. F. et al., Chem. Commun., 2019, 55, 8514;
[2] Cramer, N. et al., Angew. Chem. Int. Ed. 2018, 57, 11040;
[3] Yamaguchi, J.; Itami, K. et al., Chem. Sci., 2012, 3, 2165.

Synthesis and Characterization of new chiral Bifunctional NHC-Complexes

N. E. Niggli[1], O. Baudoin[1]*

[1]Department of Chemistry, University of Basel

Despite numerous attempts, the use of either known chiral ancillary ligands, chiral bases or chiral bifunctional ligands allows only a limited access to enantioenriched C-H activation/functionalization products so far.[1] Striving for a broader applicability of enantioselective C-H activation, new catalytic systems must be developed and investigated. The use of NHC-type ligands is known to result in high activity and enantioselectivity in Pd(0)-catalyzed C(sp^3)-H activation. For more simple substrates, it was shown that chiral NHC-type ligands can compete with more commonly applied phosphorus type ligands.[1][2] Some previous results in our group even demonstrate the superiority of such NHC-type ligands in terms of activity, selectivity and enantioselectivity in more difficult C(sp^3)-H activations.[3] This, together with the improved efficiency and enantioselectivity induced by bifunctional phosphine/carboxylate ligands over the corresponding monofunctional ones,[4] led us to the synthesis and characterization of a small library of new bifunctional NHC-ligands (**A**) and their corresponding well-organized DMBPA[5]-palladacycles (**CA**). It is believed that the innate nature of the NHC-core together with the highly organized structure of the complex might show highly beneficial effects in the enantioselective C-H functionalization allowing the access to new enantioenriched compounds.



[1] Christopher G. Newton, Shou-Guo Wang, Caio C. Oliveira, Nicolai Cramer, *Chem. Rev.* **2017**, 117, 8908–8976.
[2] Masafumi Nakanishi, Dmitry Katayev, Céline Besnard, E. Peter Kündig,*Angew. Chem. Int. Ed.* **2011**, 50, 7438–7441.
[3] Romain Melot, Marco Zuccarello, unpublished results.
[4] Lei Yang, Markus Neuburger, Olivier Baudoin, *Angew. Chem. Int. Ed.* **2018**, 57, 1394–1398.
[5] Mihai S. Viciu, Roy A. Kelly III, Edwin D. Stevens, Frédéric Naud, Martin Studer, Steven P. Nolan, *Org. Lett.* **2003**, 5, 1479–1482.

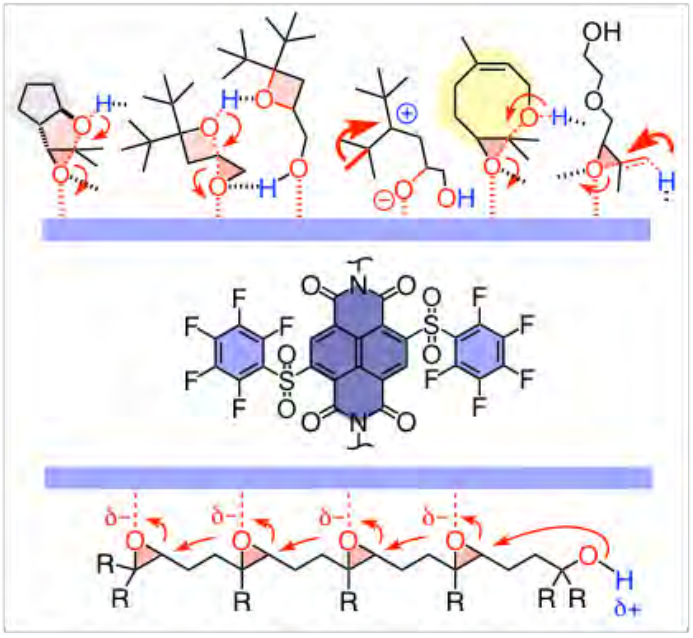
Primary Anion-π Catalysis of Epoxide-Opening Ether Cyclizations: Access to New Reactivity and Natural Product Inspired Cascades

M. Paraja[1], X. Hao[1], S. Matile[1]*

[1]Department of Organic Chemistry, University of Geneva, Geneva, Switzerland

The term anion-π catalysis is based on the stabilization of anionic transition states on aromatic π surfaces. In the last years, many reactions have been accelerated on π acidic aromatic surfaces [1]. However particularly interesting have been the epoxide-opening ether cyclizations, because it was found to be the first primary anion-π catalysis, also showing autocatalytic behavior [2]. Although the reaction proceeds through unconventional mechanisms, the obtained products are the same as those from conventional Brønsted acid catalysis and in agreement with the Baldwin rules. Thus, after further investigation it was possible to report that anion-π catalysis can lead to unconventional ring chemistry furnishing a wide variety of anti-Baldwin cyclizations [3]. For smaller rings, anion-π catalysis affords anti-Baldwin oxolanes, 2-oxabicyclo[3.3.0]octane and the methyl migration for the expansion of a Baldwin oxetane. For large rings, anion-π templated autocatalysis is thought to alleviate the entropic penalty of folding to enable disfavored anti-Baldwin cyclizations into oxepanes and oxocanes.

The delocalized nature of anion-π interactions has always suggested that they should serve best in stabilizing long-distance charge displacements. Taking inspiration from steroid cyclizations, conventional trigger for cation-π biocatalyst in nature, we were capable to promote the epoxide-opening ether cyclizations of oligomers up to tetramers towards anionπ catalysis [4]. hese natural products inspired polyether cascade cyclizations proceed with exceptionally high autocatalysis (rate enhancements $k_{auto}/k_{cat} > 10^4$ M^{-1}) which opens up interesting perspectives for future.



[1] Y. Zhao, Y. Cotelle, L. Liu, J. López-Andarias, A. B. Bornhof, M. Akamatsu, N. Sakai, S. Matile, *Acc. Chem. Res*, **2018**, *51*, 2255-2263.
[2] X. Zhang, X. Hao, L. Liu, A.-T. Pham, J. López-Andarias, A. Frontera, N. Sakai, S. Matile, *J. Am. Chem. Soc*, **2018**, *140*, 17867-17871.
[3] M. Paraja, S. Matile, *Angew. Chem. Int. Ed.* **2020**, *59*, 6273-6277.
[4] M. Paraja, X. Hao, S. Matile, *Angew. Chem. Int. Ed*, DOI: 10.1002/anie.20200681.

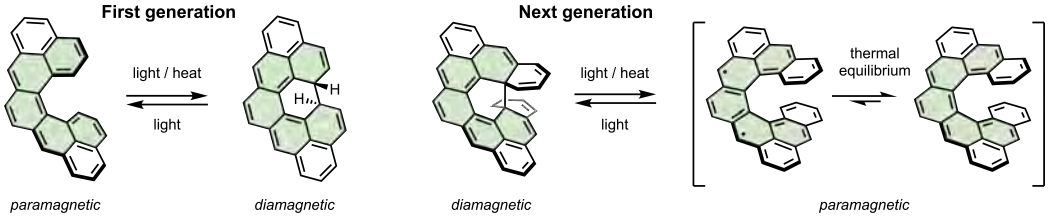
Cethrenes – Chiroptical & magnetic switches for supramolecular conductive assemblies

T. Pastierik[1], P. Ribar[2], C. Schuppisser[1], M. Juríček[1]*

[1]Department of Chemistry, University of Zurich, Winterthurerstrasse 190, CH-8057, Zürich, [2] Department of Chemistry, University of Basel, St. Johanns-Ring 19, CH-4056, Basel

The discovery of conjugated carbon allotropes – fullerenes, carbon nanotubes, and graphene – unleashed the unique electronic properties of these materials, earning them the status quo as the future of the electronics. Over the years, these hopes turned into reality, and carbon-based materials found their way into artificial systems that mimic photosynthesis or into photovoltaic devices. The latter application is an example that already earns money on the markets. The possibility of using graphene in digital electronics was demonstrated by the construction of a graphene-based field-effect transistor, which was driven by its extreme current-carrying capacity, charge-transfer mobility, and ultimately low thickness.[1] The cost-effective preparation of well-defined large carbon structures remains, however, an enormous challenge. To address this challenge, our group employs small, well-defined fragments of conjugated carbon allotropes to build large assemblies of magnetic and conductive materials.

Open-shell graphene fragments were shown to form self-assembled wires, which display conductivity that is superior to their closed-shell analogues.[2] In our group, we took this concept further by designing a helical diradicaloid system that acts as a switch between an open paramagnetic and a closed diamagnetic form.[3,4] Such molecular systems can deliver materials, where magnetism and conductivity can be switched ON and OFF. The first generation of this switch, [75]cethrene (figure, top left), proved to be magnetically active, but the closed-form readily oxidized to a flat hydrocarbon, which did not allow us to explore the potential of this molecule further.[5] In my talk, I will present synthesis and study of the next generation switch – dibenzo[75]cethrene (figure, top right) – immune to oxidation and show its potential to yield responsive supramolecular assemblies.



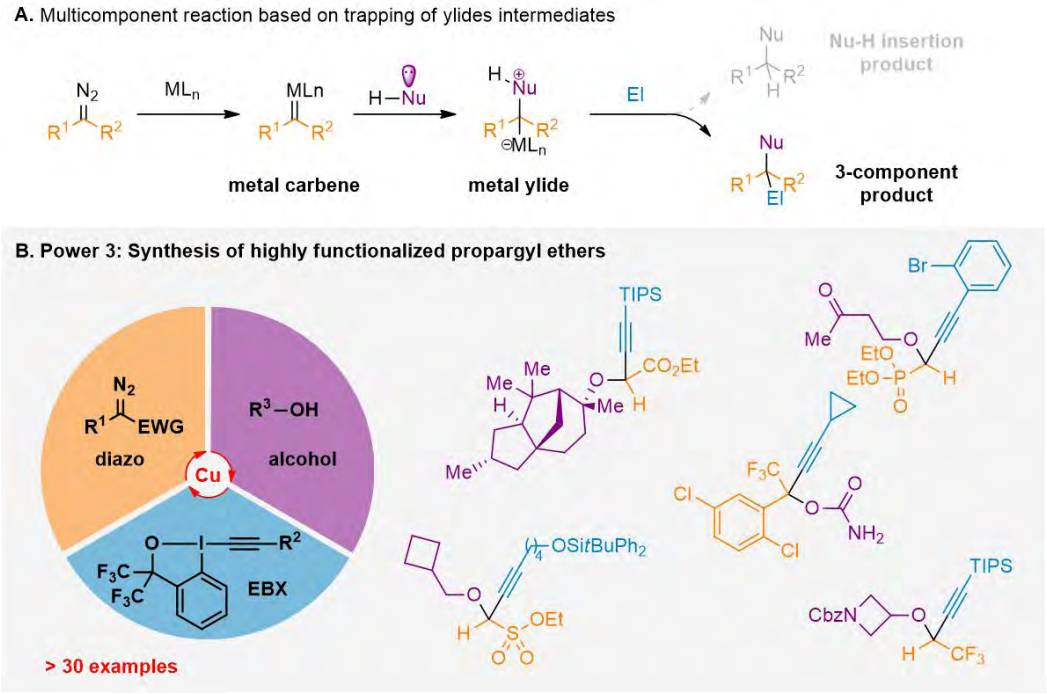
[1] A. Hirsch, *Nat. Mater.*, **2010**, *9*, 868–871
[2] T. Kubo, A. Shimizu, M. Sakamoto, M. Uruichi, K. Yakushi, M. Nakano, D. Shiomi, K. Sato, T. Takui, Y. Morita, K. Nakasuji, *Angew. Chem. Int. Ed.*, **2005**, *44*, 6564–6568
[3] T. Šolomek, P. Ravat, Z. Mou, M. Kertesz, M. Juríček, *J. Org. Chem.*, **2018**, *83*, 4769–4774
[4] P. Ravat, T. Šolomek, D. Häussinger, O. Blacque, M. Juríček, *J. Am. Chem. Soc.*, **2018**, *140*, 10839–10847
[5] P. Ravat, T. Šolomek, M. Rickhaus, D. Häussinger, M. Neuburger, M. Baumgarten, M. Juríček, *Angew. Chem. Int. Ed.*, **2016**, *55*, 1183–1186

Three-Component Oxy-Alkynylation of Diazo Compounds: Synthesis of Highly Functionalized Propargyl Ethers[1]

G. Pisella[1], A. Gagnebin[1], J. Waser[1]*

[1]Laboratory of Catalysis and Organic Synthesis (LCSO), EPFL

Multicomponent reactions provide efficient means to access molecular complexity.[2] In this context, transient ylide intermediates generated from the insertion of protic nucleophiles (alcohols, amines, thiols and aromatic compounds) into metal-carbenes generated from diazo compounds have been intercepted with various electrophiles (carbonyl compounds, imines, Michael acceptors,...) to afford valuable three-component products (Scheme 1A).[3] To further expand the use of such multicomponent strategy, we developed a copper-catalyzed oxy-aylkynylation of diazo compounds using alcohols and ethynylbenziodoxolone (EBX) reagents as partners for the construction of highly functionalized propargyl ethers (Scheme 1B).



The three components of the reactions can be extensively varied, leading to a broad range of products with high structural diversity. In particular, primary, secondary and tertiary alcohols, as well as, various important functional groups (including alkene, alkyne, fluoro, chloro, bromo, ether, ester, ketone, carbamate, imide, cyano, boronic ester and heterocyclic groups) were well tolerated, which would be difficult to achieve using traditional etherification methods under strongly basic or acidic conditions. The transformation can be performed using simple copper salts as catalyst, and does not require the use of one of the partners in large excess. The reaction is speculated to proceed via a copper oxonium ylide intermediate.
Further discussion about this work will be possible through Zoom on Tuesday 25.08.2020, 12:15-13:15.

[1] G. Pisella, A. Gagnebin, J. Waser *Chem. Eur. J.* **2020**, doi: 10.1002/chem.202001317.
[2] *Multicomponent Reactions*, Ed. J. Zhu, H. Bienaymé, Wiley-VCH Verlag, **2005**.
[3] a) X. Guo, W. Hu, *Acc. Chem. Res.* **2013**, *46*, 2427-2440; b) D. Zhang, W. H. Hu, *Chem. Rec.* **2017**, *17*, 739-753.

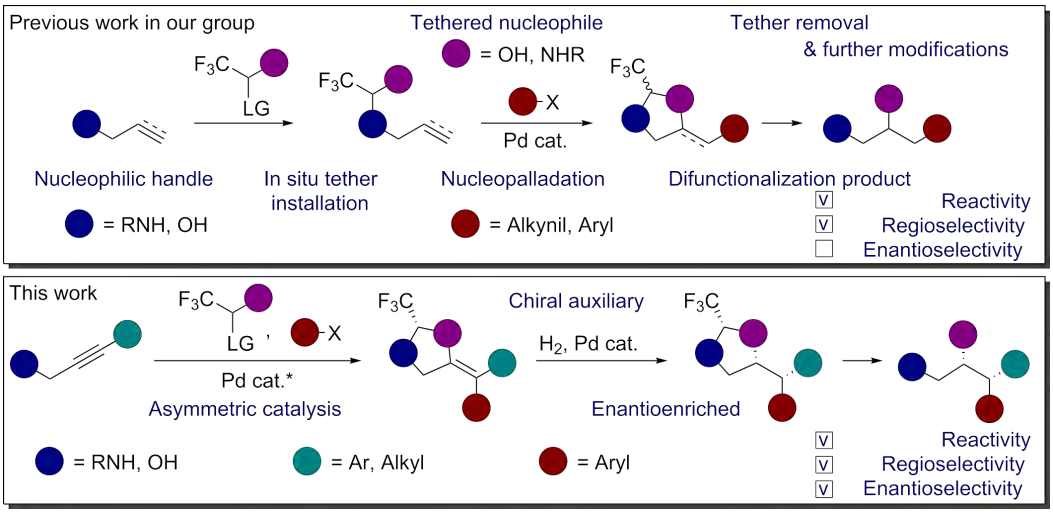
Molecular tethering for Pd catalyzed stereoselective difunctionalization of unsaturated systems

M. Purins[1], L. Buzzetti[1], P. Greenwood[1], J. Waser[1]*

[1]Laboratory of Catalysis and Organic Synthesis (LCSO), Institute of Chemical Sciences and Engineering (ISIC), EPFL

Difunctionalization of double bonds is a facile way to build up molecular complexity starting from abundant, easily accessible feedstock chemicals. However, for non-activated or unbiased substrates, it is difficult to achieve high levels of reactivity and selectivity.[1] Therefore, alternative methods for selective difunctionalization of olefins are highly desirable. In the last years, our group has tackled the problem of selective nucleopalladation of unsaturated systems. We have recently developed an *in situ* tethering approach using trifluoracetaldehyde derived electrophilic compounds as molecular tethers. The nitrogen or oxygen of the abundant allyl amines and alcohols were used as handles for the installation of an intramolecular nucleophilic center directing the Pd catalyzed difunctionalization reactions.[2-4] Remarkably, the installed tether can be easily hydrolyzed to reveal the important 1,2-aminoalcohol and 1,2-diamine scaffolds. This tethering concept was extended to the difunctionalization of triple bonds to synthesize highly substituted enynes and complex α-amino ketone derivatives.[5]

Herein, we will present our efforts towards the development of an enantioselective tethered carboetherification of propargyl amines. Our approach exploits asymmetric catalysis to access tetrasubstituted olefins substituted with an enantioenriched chiral oxazolidine core, which can be exploited as temporary chiral auxiliary for directing the following asymmetric hydrogenation and access enantioenriched amino alcohols precursors. Discussion about this research will be possible via zoom meeting on Tuesday 25.08.2020, 12:15-13:15.[6]



[1] McDonald, R. I.; Liu, G.; Stahl, S. S. *Chem. Rev.* **2011**, 111, 2981–3019.
[2] Orcel, U.; Waser, J. *Angew. Chem. Int. Ed.* **2015**, 54, 5250–5254.
[3] Orcel, U.; Waser, J. *Angew. Chem. Int. Ed.* **2016**, 55, 12881–12885.
[4] Muriel, B.; Orcel, U.; Waser, J. *Org. Lett.* **2017**, 19, 3548–3551.
[5] Greenwood, P. D. G.; Grenet, E.; Waser, J. *Chem. Eur. J.* **2019**, 25, 3010–3013.
[6] The link will be available on the following document shortly before: https://drive.google.com/file/d/1s1Tg48ABj5q010FyUV29sckTHGopQv6o/view?usp=sharing

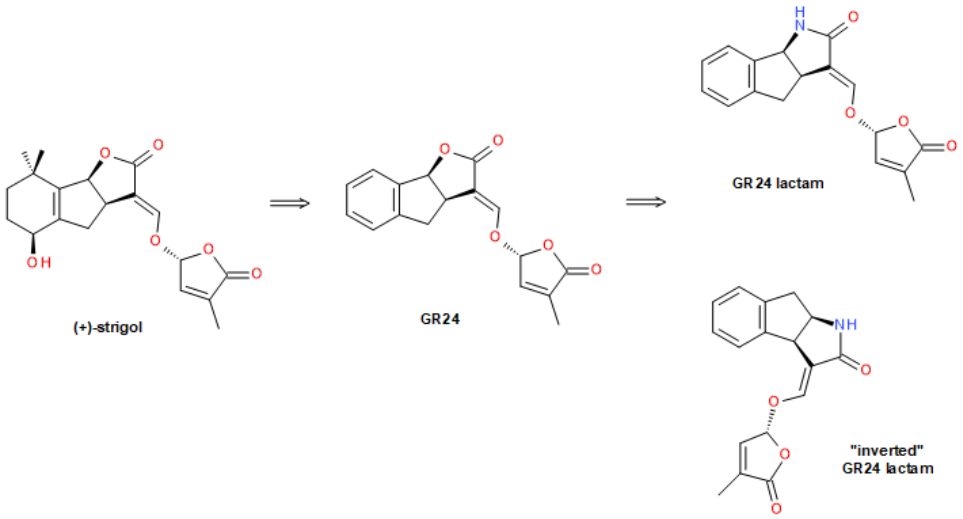
Synthesis and biological profile of all stereoisomers of GR24-lactam and analogues

P. Quinodoz[1], A. Lumbroso[1], M. Lachia[1], C. Screpanti[1], S. Rendine[1], S. Catak[2], R. Fonné-Pfister[1], K. Hermann[1], A. De Mesmaeker [1]*

[1]Syngenta Crop Protection AG, [2]Bogazici University, Istanbul, Turkey

The signaling properties of Strigolactones (SLs) and their multiple roles in the development of plants has raised the interest of the plant science community for more than ten years. Developing the use of these phytohormones for crop enhancement and abiotic stress management purposes would be a key technology to improve the resilience and guarantee the sustainability of agriculture in the future [1].

In this context, the design and synthesis of natural SLs and derivatives will be presented [2] [3], especially the lactam analogues of GR24, a common synthetic SL derived from (+)-strigol (see scheme below). The synthesis of these strigolactams [4], harnessing the chemistry of keteniminum salts, will be disclosed, as well as their activity in biological assays. In particular, the crucial influence of stereochemistry will be highlighted by comparing the biological profile of the different stereoisomers.



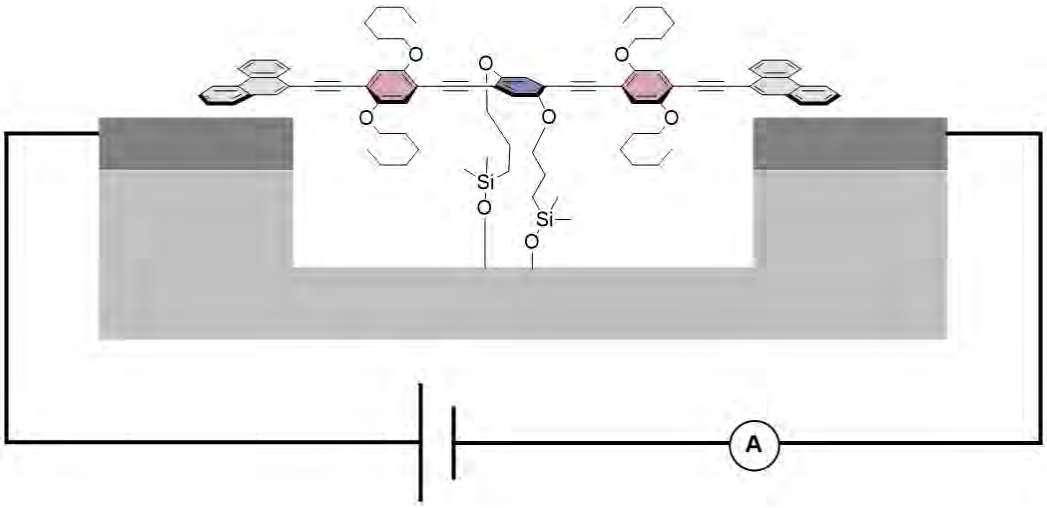
[1] A. De Mesmaeker, C. Screpanti, R. Fonné-Pfister, M. Lachia, A. Lumbroso, H. Bouwmeester, *Chimia*, **2019**, 73, 7/8, 549-560
[2] M. Lachia, H.Ch. Wolf, P. J. M. Jung, C. Screpanti ,A. De Mesmaeker,*Bio. Org. Med. Chem.*, **2015**, 25, 2184–2188
[3] M. Yoshimura, M. Dieckmann, P.Y.-Dakas, R. Fonné-Pfister, K. Hermann, S. Rendine, P. Quinodoz, B. Horoz, S. Catak, A. De Mesmaeker, *Helv. Chim. Acta*, **2020**, 103, e2000017
[4] M. Lachia, H.Ch. Wolf, P. J. M. Jung, C. Screpanti ,A. De Mesmaeker, Bio. Org. Med. Chem., 2015, 25, 2184–2188t Lumbroso, E. Villedieu-Percheron, D. Zurwerra, C. Screpanti, M. Lachia, P.-Y. Dakas, L. Castelli, V. Paul, H. C. Wolf, D. Sayer, A. Beck, S. Rendine, R. Fonné-Pfister, A. De Mesmaeker, *Pest. Manag. Sci.*, **2016**, 72, 11, 2054-2068

Tailor-Made Molecular Rods for Graphene Junctions

K. Reznikova[1], L. Delarue Bizzini[1], M. El Abbassi[2], O. Schmuck[3,4], A. Christy[1], D. Häussinger[1], M. Neuburger[1], M. Calame[3,4], M. Mayor[1,5]*

[1]Department of Chemistry, University of Basel, [2]Delft University of Technology, Faculty of Applied Science, [3]Department of Physics, University of Basel, [4]EMPA, Swiss Federal Laboratories for Materials Science and Technology, [5]Karlsruhe Institute of Technology, Institute of Nanotechnology

Graphene has been applied in several technologies since its discovery in 2004. [1] A new promising idea is to use graphene as a contact material in nanoelectronics. For this application, graphene is superior to gold because of its stability, 2D structure and large variety of possible anchoring groups. [2-3] Here, we will present the synthesis and further studies on a series of tailor-made molecular rods for graphene junctions. The desired molecules are designed to bridge a nanogap between two graphene electrodes on a silicon insulator. The molecular rod consists of a central moiety which is modified with two silica anchoring groups to prevent the molecular rod from sliding out of the junction. Oligo(phenylene-ethynylene) (OPE) linkers establish the electronic communication and outer aromatic anchoring groups contact graphene *via* π-π interactions. We propose the synthesis of a library of OPEs with different lengths, containing various aromatic groups for the deposition to the graphene surface.



[1] K. S. Novoselov, A. K. Geim, S. V. Morozov, D. Jiang, Y. Zhang, S. V. Dubonos, I. V. Grigorieva, A. A. Firsov, *Science*, **2004**, *5696*, 666–669.
[2] F. Prins, A. Barreiro, J. W. Ruitenberg, J. S. Seldenthuis, N. Aliaga-Alcane, L. M. K. Vandersypen, H. S. J. van der Zant, *Nano Lett.*, **2011**, *11*, 4607–4611.
[3] C. Nef, L. Pósa, P. Makk, W. Fu, A. Halbritter, C. Schönenberger, M. Calame, *Nanoscale*, **2014**, *6*, 7249–7254.

Enantioselective C(sp^2)-H arylation for the synthesis of warped molecules

D. Savary[1], O. Baudoin[1]*

[1]Department of Chemistry, University of Basel

Enantioselective Pd^0-catalysed C-H activation reactions rely on the use of a chiral ancillary ligand and/or a chiral base [1]. Our group recently developed a new family of chiral bifunctional phosphine-carboxylate ligands [2], which ensure high stereocontrol over the enantiodetermining CMD step, for asymmetric C(sp^2)-H arylation. Herein, we describe the application of this new approach to the first enantioselective synthesis of warped molecules.

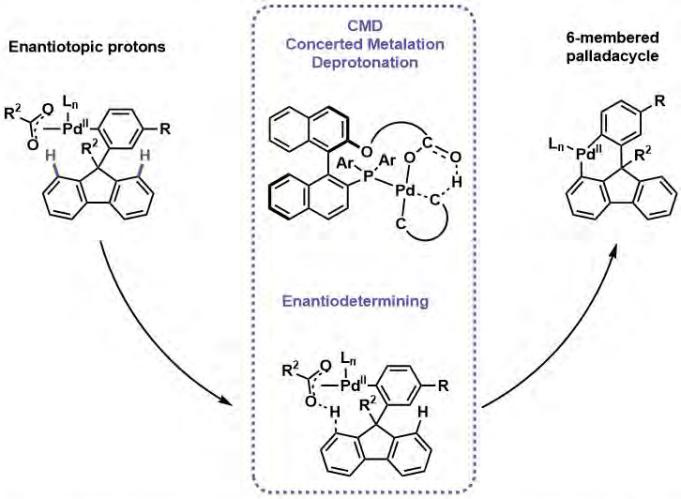


Figure 1 stereocontrol over the key CMD step resulting from a highly organised transition-state

Our catalytic system was optimised for the preparation of fluoradenes using the model substrate shown on **Figure 2**. The developed protocol was then applied to the preparation of other warped molecules in order to investigate the application scope of this transformation. Very diverse polycylic compounds could be formed in high yield and with good to excellent enantioselectivity.

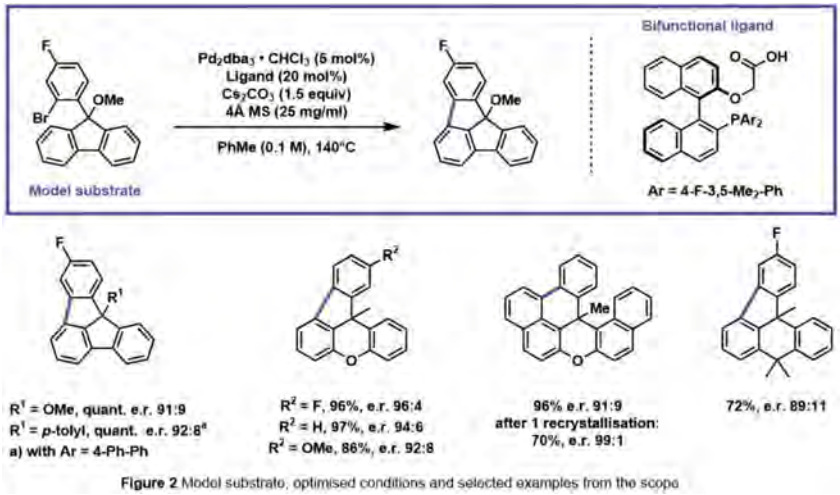


Figure 2 Model substrate, optimised conditions and selected examples from the scope

[1] a) C. G. Newton, S.-G. Wang, C. C. Oliveira, N. Cramer, *Chem. Rev.*, **2017**, 117, 8908-8976. b) T. G. Saint-Denis, R.-Y. Zhu, G. Chen, Q.-F. Wu, J.-Q. Yu, *Science*, **2018**, 359, 759-770. c) L. Yang, R. Melot, M. Neuburger, O. Baudoin, *Chem Sci.*, **2017**, 8, 1344–1349.
[2] L. Yang, M. Neuburger, O. Baudoin, *Angew. Chem. Int. Ed.*, **2018**, 57, 1394 –1398.

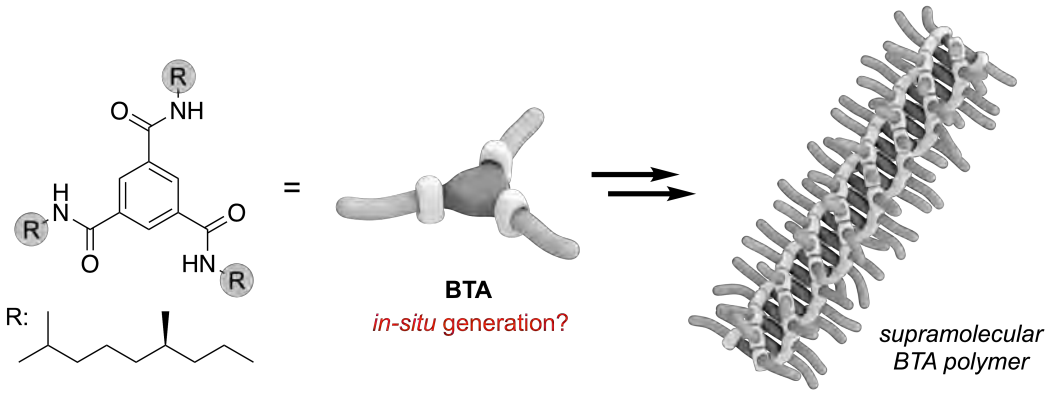
Emergence of Complex Molecular Systems *via* Combination of Covalent and Non-Covalent Synthesis

T. Schnitzer[1], E. W. Meijer[1]*

[1]Eindhoven University of Technology

Complex molecular systems are key for device miniaturization, development of energy materials and efforts to mimic biological processes.[1-3] Self-assembly, the power of molecules to autonomously form defined aggregates, is a key player in the emergence of complexity in molecular systems. Yet, the construction of such systems is not easy. Inspired by total synthesis in organic chemistry, a paradigm shift from one-step assembly to multi-step non-covalent synthesis was proposed: Complex molecular systems are not obtained in a single non-covalent assembly step, but rather in a combination of covalent and non-covalent reaction steps.[4] This raises the question how to perform covalent organic reactions in combination with supramolecular structures. This is challenging because supramolecular structures are often assembled by weak forces, in continuous dynamic exchange and are highly sensitive to environmental changes.[1-4] Thus, supramolecular substrates are difficult targets for common organic syntheses.

Here, we present new synthetic strategies for supramolecular assemblies using a combination of covalent and non-covalent chemistry. The well-studied helical assembling of 1,3,5-benzenetricarboxamide (BTA) type monomers served as model system. The *in-situ*generation of BTA monomers in a multi-component assembly was investigated, focusing on the interplay between reaction kinetics of the covalent bond formation and the non-covalent assembling process. In addition, the assemblies derived from pre-formed BTA monomers versus in-situ generated BTAs were investigated to gain a deeper understanding on the fundamentals of such multi-component assemblies.



[1] J. F. Lutz, J. M. Lehn, E. W. Meijer, K. Matyjaszewski, *Nature Reviews Materials* **2016**, *1*, 16024.
[2] T. Aida, E. W. Meijer, S. I. Stupp, *Science* **2012**, *335*, 6070.
[3] T. Aida, E. W. Meijer, *Isr. J. Chem.* **2020**, *60*, 33.
[4] G. Vantomme, E. W. Meijer, *Science* **2019**, *363*, 6434.

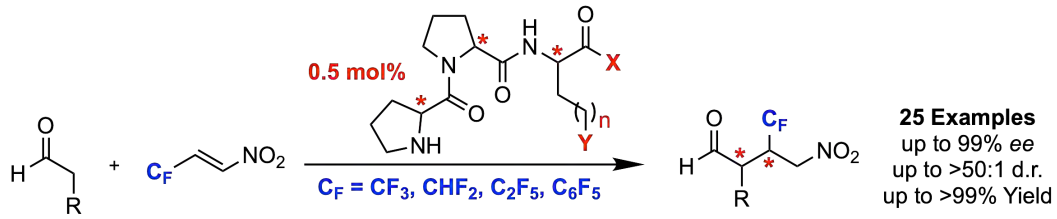
Peptide catalyzed stereoselective conjugate addition reaction of aldehydes to fluorinated nitroolefins.

M. Schnurr[1], H. Wennemers[1]*

[1]Laboratory of Organic Chemistry, D-CHAB, ETH Zurich, Switzerland

Tripeptides of the H-Pro-Pro-Xaa type are highly reactive and stereoselective catalysts for asymmetric aldol reactions[1] and conjugate addition reactions of carbonyl compounds to nitroolefins[2-4], dicyanoolefins[5] and maleimide.[6] For example, as little as 0.1 mol% H-DPro-Pro-Glu-NH_2 suffices to catalyze conjugate addition reactions of aldehydes to nitroolefins in high yields and excellent stereoselectivities.[7]

Herein we present the stereoselective conjugate addition of aldehydes to fluorinated nitroolefins, a highly reactive class of electrophiles which usually deactivate secondary amine based organocatalysts by *N*-alkylation. By using peptide catalysts, we were able to overcome this deactivation and perform the reaction with only 0.5 mol% catalyst, while maintaining high yield and stereoselectivity.



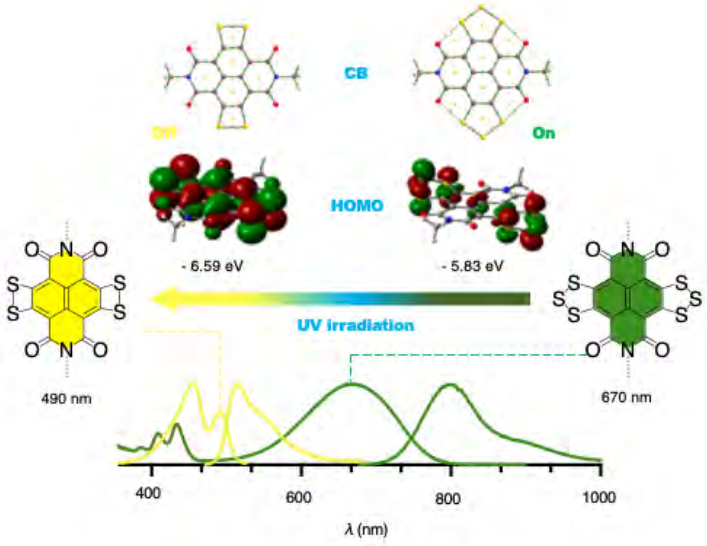
[1] P. Krattiger, R. Kovasy, J. D. Revell, S. Ivan, H. Wennemers, *Org. Lett.* **2005**, *7*, 1101–1103.
[2] M. Wiesner, J. D. Revell, H. Wennemers, *Angew. Chem. Int. Ed.* **2008**, *120*, 1897–1900.
[3] J. Duschmalé, H. Wennemers, *Chem. Eur. J.* **2012**, *18*, 1111–1120.
[4] R. Kastl, H. Wennemers, *Angew. Chem. Int. Ed.* **2013**, *52*, 7228–7232.
[5] T. Schnitzer, H. Wennemers, *Synlett* **2017**, *28*, 1282–1286.
[6] C. E. Grünenfelder, J. K. Kisunzu, H. Wennemers, *Angew. Chem. Int. Ed*. **2016**, *55*, 8571–8574.
[7] M. Wiesner, G. Upert, G. Angelici, H. Wennemers, *J. Am. Chem. Soc.* **2010**, *132*, 6–7.

Green, π-Acidic Naphthalenediimides with Oligosulfides in Their Core

I. Shybeka[1], A. Aster[1], N. Sakai[1], A. Frontera[2], E. Vauthey[1], S. Matile[1]*

[1]School of Chemistry and Biochemistry, University of Geneva, [2]University of the Balearic Islands

Naphthalenediimides (NDIs) have been known to be used for different applications: sensors, artificial photosystems, ion channels, catalysis through anion−π interactions, intercalations with DNA for biological application [1]. The chemistry of core-substituted NDIs is colorful and single-atom substitutions are already enough to cover the primary colors [2]. Herein we present NDIs with cyclic oligochalcogenides (COCs) in their core. NDI-bis(trithiole)s are green, absorb at 670 nm. This record red shift occurs because chalcogen bonds (CB) [3] from the imides inject sufficient electron density to shift the HOMO from the aromatic core to the trisulfide. Excited at 300 nm, they contract into NDI-bis(dithiete). Ring-tension in disulfide mediated chalcogen bond cleavage and promote blue shift to 494 nm. NDI-bis(trithiole)s are reactive with thiols and they show high retention on thiol-exchange affinity columns compared to other cyclic oligochalcogenides (COCs) [4]. This makes COC-NDIs interesting not only for established applications, but also for the penetration of living cells.



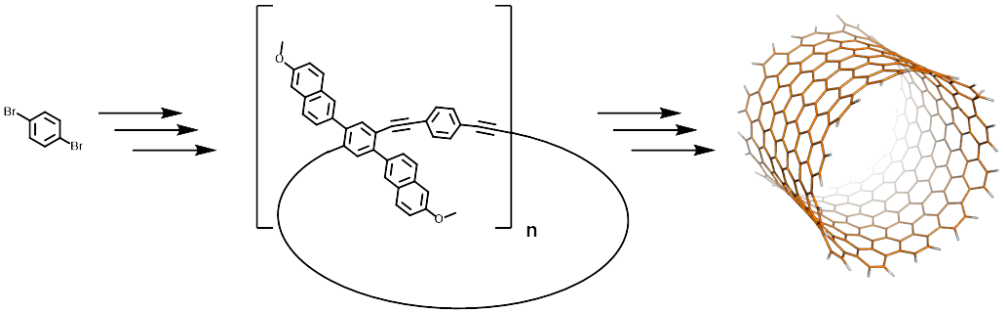
[1] M. Al Kobaisi, S.V. Bhosale, K. Latham, A. M. Raynor, S. V. Bhosale, *Chemical Reviews,* **2016**, 116, 11685–11796.
[2] N. Sakai, J. Mareda, E. Vauthey, S. Matile, *Chemical Communications,* **2010**, 46, 4225.
[3] L. Vogel, P. Wonner, S. M. Huber, *Angewandte Chemie International Edition,* **2019**, 58, 1880–1891.
[4] Y. Cheng, L. Zong, J. López-Andarias, E. Bartolami, Y. Okamoto, T. R. Ward, N. Sakai, S. Matile, *Angewandte Chemie International Edition,* **2019**, 58, 9522–9526.

Towards Molecular Graphene Belts and Möbius Strips

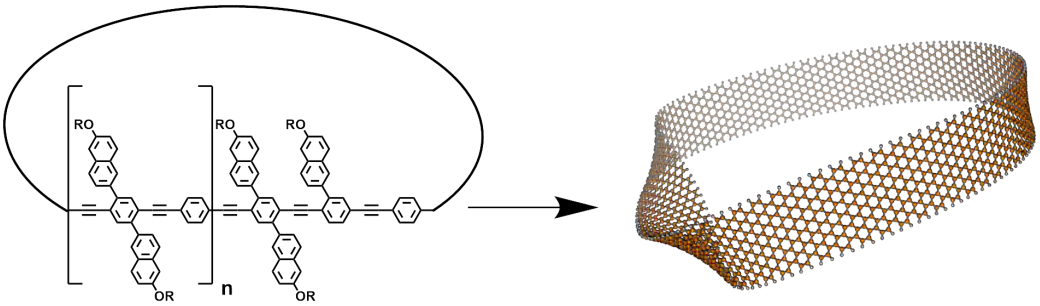
E. Sidler[1], M. Mayor[1]*

[1]University of Basel, Department of Chemistry

The synthesis of topological interesting carbon architectures has sparked the interest of many scientists and especially the defined bottom-up synthesis of carbon nanotubes (CNTs) is highly sought after. Our work towards large molecular ring structures for the investigation of persistent currents has brought us to the challenge of synthesizing armchair CNTs.[1] Due to the limitations of available state of the art magnetic field strengths, persistent current investigations are limited to rings with diameters of 10 nm and above, therefore increasing the difficulty of their fabrication. Based on the synthesis of armchair graphene sheets by Dichtel and co-workers, we envision to synthesize the CNT from the similar oligo(*p*-phenylene ethynylene) (OPE) joined into a strained macrocycle.[2] The OPE backbone consists of alternating phenyls and 2,5-naphthyl substituted phenyls connected by alkyne units.[3] Transformation of the alkynes by benzannulation followed by Scholl oxidation allows the formation of the fully fused graphene belt.[4] To induce the strain into the backbone and favor the macrocyclization, angled corner units, specifically 1,4-cyclohexadiene units, are inserted strategically. Signficant achievements towards the synthetic goal have already been made and small OPE macrocycles were synthesized as test systems.



Additionally, a strategy to synthesize a Möbius strip of an armchair CNT was developed. A targeted insertion of an asymmetric OPE subunit should inhibit the formation of the graphene sheet without twisting the whole unit by 180°, therefore forming the Möbius topology. The increased strain due to the 180° twist will presumably allow the Möbius topology only for large systems, further increasing the challenge of its synthesis.



[1] Mayor, C. Didschies, *Angew. Chem. Int. Ed.,* **2003**, 42, 3176-3179.
[2] J. Gao, F. J. Uribe-Romo, J. D. Saathoff, H. Arslan, C. R. Crick, S. J. Hein, B. Itin, P. Clancy, W. R. Dichtel, Y. Loo, *ACS Nano,* **2016,** 10, 4847-4856.
[3] H. Arslan, J. D. Saathoff, D. N. Bunck, P. Clancy, W. R. Dichtel, *Angew. Chem.,* **2012**, 124, 12217-12220.
[4] N. Asao, T. Nogami, S. Lee, Y. Yamamoto, *J. Am. Chem. Soc.,* **2003**, 125, 10921-10925.

A highly sensitive and selective colorimetric and fluorescent sensor for phosgene detection

A. B. Solea[1,2], A. Crochet[2], C. Allemann[1], K. M. Fromm[2], O. Mamula[1]*

[1]Haute Ecole d'Ingénierie et d'Architecture de Fribourg, HES-SO University of Applied Sciences Western Switzerland, Pérolles 80, CH-1705 Fribourg, Switzerland, [2]University of Fribourg, Department of Chemistry, Chemin du Musée 9, CH-1700 Fribourg, Switzerland

Phosgene is a highly toxic and reactive gas that was extensively used in World War I as a chemical weapon. Its toxicity is due to the disruption of the air-blood barrier in the pulmonary alveoli which leads to pulmonary edema and eventually death.[1] Despite its toxicity, phosgene is vastly employed as a starting material in the chemical industry for the production of pharmaceuticals and isocyanates.[2] Hence, its fast and precise detection is of high importance not only for the protection of the operators involved in the industrial processes, but also for the general safety in case of terrorist attacks or accidents.

We have developed a highly sensitive and selective phosgene sensor based on a carboxylic acid derivative of phenyl 5,6-pinenepyridine (**1**), which shows fast response in solution and solid state (Figure 1A). The sensor displays both colorimetric and fluorescent response in the presence of phosgene (Figure 1B), leading to an isoindolone-derivative (**2**), as demonstrated by single-crystal X-Ray diffraction (Figure 1C). The proposed mechanism for the synthesis of **2** involves the formation of an acyl chloride, followed by a nucleophilic attack from the pyridine. This is the first example of such a sensing reaction for phosgene detection, as most of the reported sensors are based on the formation of urea derivatives starting from diamines.[3–5]

With a limit of detection in solution in the order of 1 ppb, our phosgene sensor is one of the most sensitive reported up to date. In addition, a range of chlorinated compounds was tested and the compound **1** has shown to be very specific in its response towards phosgene. In this contribution, we will present complete studies on the synthesis of the sensor as well as the analytical and photophysical details of the sensing reaction.

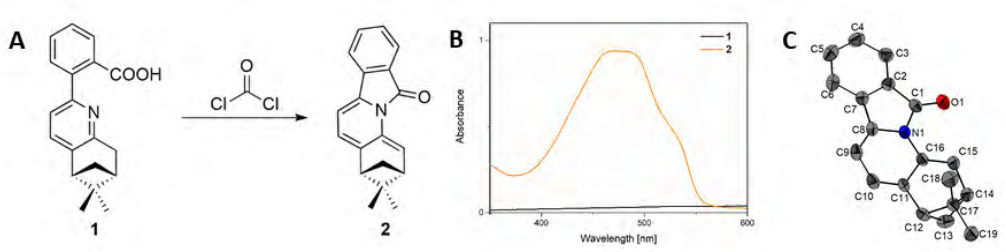


*Figure 1. The sensing reaction (A). UV-Vis spectra of **1** and **2** in THF, at 0.1 mM concentration (B). X-ray structure of **2**, with thermal ellipsoids at 30% probability (the hydrogen atoms were omitted for clarity) (C).*

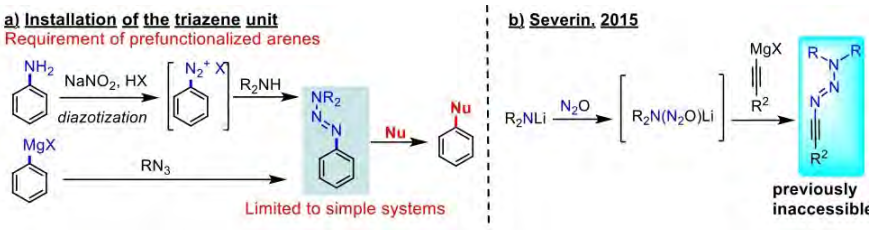
[1] W. Li, F. Liu, C. Wang, H. Truebel, J. Pauluhn, *Toxicol. Sci.* **2013**, *131*, 612–628.
[2] J. J. Collins, D. M. Molenaar, L. O. Bowler, T. J. Harbourt, M. Carson, B. Avashia, T. Calhoun, C. Vitrano, P. Ameis, R. Chalfant, et al., *J. Occup. Environ. Med.* **2011**, *53*, 239–244.
[3] L. Chen, D. Wu, J.-M. Kim, J. Yoon, *Anal. Chem.* **2017**, *89*, 12596–12601.
[4] S.-L. Wang, L. Zhong, Q.-H. Song, *Chem. Commun.* **2017**, *53*, 1530–1533.
[5] H. Xie, Y. Wu, F. Zeng, J. Chen, S. Wu, *Chem. Commun.* **2017**, *53*, 9813–9816.

Highly Divergent Access to Densely Substituted Arenes, Pyridines and Pyridones *via* Transition Metal-Catalyzed Transformations of Alkynyl Triazenes

J. F. Tan[1], C. T. Bormann[1], F. Perrin[1], M. F. Chadwick[1], K. Severin[1]*, N. Cramer[1]*

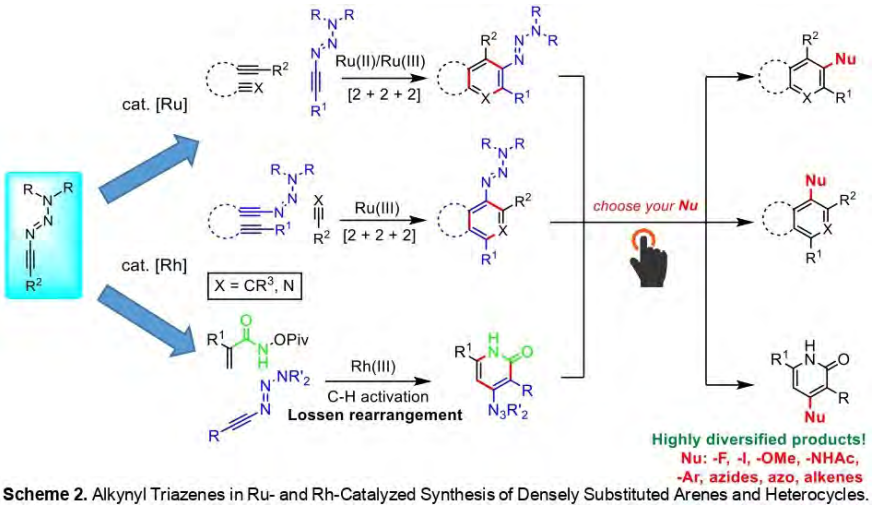
[1]EPFL Lausanne, Switzerland

Given their unique property as a stable aryl diazonium surrogate, aryl triazenes have garnered great attention with their versatility in organic synthesis. However, the access to such aryl triazenes requires an already appropriately prefunctionalized aryl precursor, such as anilines or aryl magnesium salts (**Scheme 1a**). This severely limits exploitation of the triazene functionality, particularly if the targeted scaffolds feature complex substitution patterns or heterocyclic structures. To further expand on the synthetic potential of aryl triazenes, complementary methods without the requirement of prefunctionalized arenes would be highly sought after.



Scheme 1. (a) Conventional Approaches for Aryl Triazene Synthesis. (b) Alkynyl Triazene Synthesis by Severin.

In this respect, we report applications of alkynyl triazenes[1] (**Scheme 1b**) in transition metal-catalyzed cyclizations and C-H activations. Specifically, we utilized ruthenium and rhodium catalysis to rapidly generate complex and densely substituted aryl and heteroaryl triazenes, including pyridines and pyridones (**Scheme 2**).[2,3] These reactions are all characterized by very pronounced regioselectivities induced by the triazenyl group. Under acidic conditions, the precisely installed triazene moiety on the ring system is smoothly converted into a wide ranging array of important aryl substituents, including fluorides. This methodology offers late-stage, highly divergent functional group manipulations on these biologically relevant heterocyclic framework, which opens up a novel and expedient avenue for medicinal chemistry studies.



Scheme 2. Alkynyl Triazenes in Ru- and Rh-Catalyzed Synthesis of Densely Substituted Arenes and Heterocycles.

[1] Gregor Kiefer, Tina Riedel, Paul Dyson, Rosario Scopelliti, Kay Severin, *Angewandte Chemie International Edition*, **2015,** 54, 302-305.
[2] Jin-Fay Tan, Carl Thomas Bormann, Florian Perrin, Mark Chadwick, Kay Severin, Nicolai Cramer, *Journal of American Chemical Society*, **2019,** 141, 10372-10383.
[3] Jin-Fay Tan, C. T. Bormann, K. Severin, N. Cramer, *ACS Catalysis*, **2020,** 10, 3790-3796.

Synthesis and Characterisation of Metallo-Porphyrin Dyads

J. Thiede[1], R. Ingle[2], M. Chergui[2], S. Liu[1], R. Häner[1]*

[1]Department of Chemistry and Biochemistry, University of Bern, Freiestrasse 3, 3012 Bern, Switzerland, [2]Laboratory of Ultrafast Spectroscopy LSU, École polytechnique fédérale de Lausanne, Station 3, CH-1015 Lausanne

In comparison to other chromophores, porphyrins show very distinct photophysical and electrochemical features. Their redox and optical properties can easily be tuned by substitutions on the central porphyrin core, as well as by the insertion of a different metal ion in the cavity.[1–3] In this work, we have prepared four different dyads (Figure 1), where two metalloporphyrin units are connected either directly or *via* a phenylene linker at their *meso*-positions. A discrepancy in electronic and Coulombic interactions between two porphyrin cores is unambiguously demonstrated by cyclic voltammetry, UV-Vis absorption and fluorescence emission spectra. All these results will be presented and discussed in the virtual poster video.

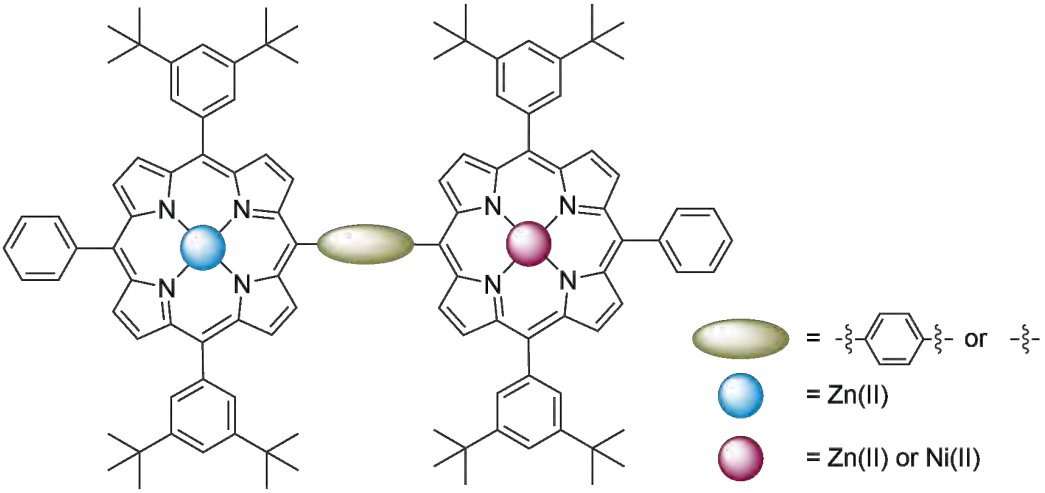


Figure 1: Schematic representation of the porphyrin dyads.

[1] Fabrice Odobel, S. Suresh, Errol Blart, Yohann Nicolas, Jean-Paul Quintard, Pascal Janvier, Jean-Yves Le Questel, David Rondeau, Pascal Richomme, Tilmann Häupl, Staffan Wallin, Leif Hammarström, Chemistry a European Journal, 2002, 8, 3027-3046.
[2] Jacob J. Piet, Peter N. Taylor, Harry L. Anderson, Atsuhiro Osuka, and John M. Warman, Journal of the American Chemical Society 2000, 122 (8), 1749-1757.
[3] Jon-Paul Strachan, Steve Gentemann, Jyoti Seth, William A. Kalsbeck, Jonathan S. Lindsey, Dewey Holten, and David F. Bocian, Inorganic Chemistry, 1998 37 (6), 1191-1201.

Continuous flow chemistry methodologies to support UCB drug discovery

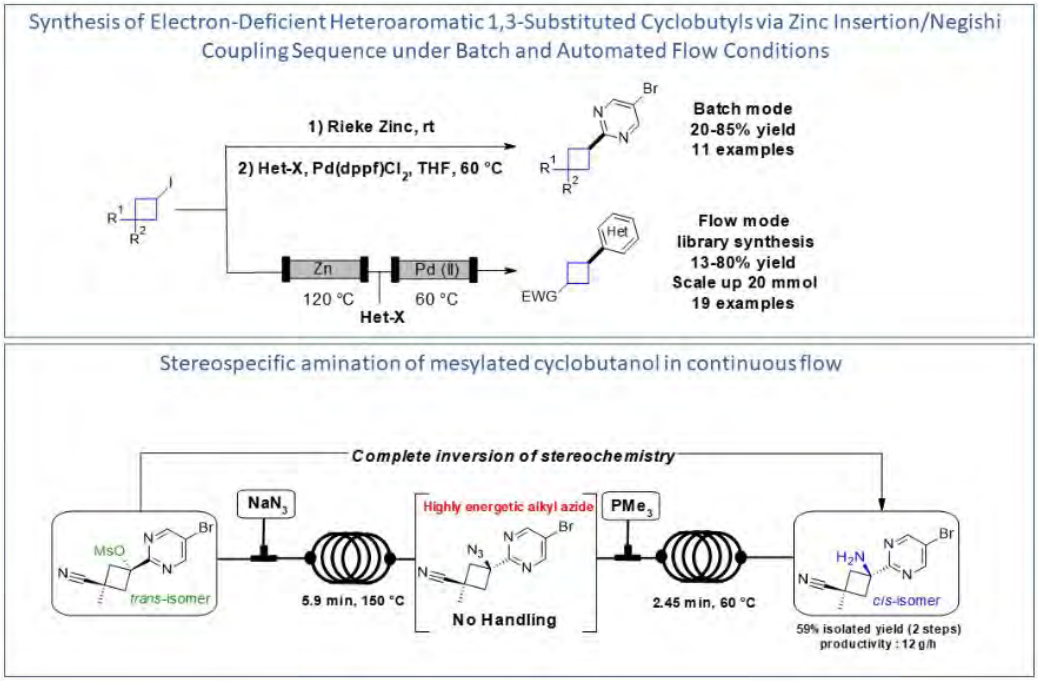
M. Tissot[1]

[1]UCB Biopharma SRL, Belgium

Herein, we will present two distinct flow methodologies towards the synthesis of 1,3-disubstituted cyclobutyls.

The first method involves the development of a new organometallic methodology to introduce various unprecedented functionalised small cycloalkyls to heteroaromatics. In a first time, this method has been developed in batch mode and then successfully transferred to a continuous process (Scheme 1). In order to allow medicinal chemists to generate rapidly libraries with this medicinally interesting moiety, we extended the process to an automated platform.[1]

The second method involves an amination of mesylated cyclobutanol enabled by a multistep continuous flow process. The flow sequence involved an azidation followed by a Staudinger reduction which avoids the handling and isolation of a hazardous alkyl azide compound (Scheme 2). The process is stereospecific with the azidation step proceeding to complete stereochemical inversion.[2]



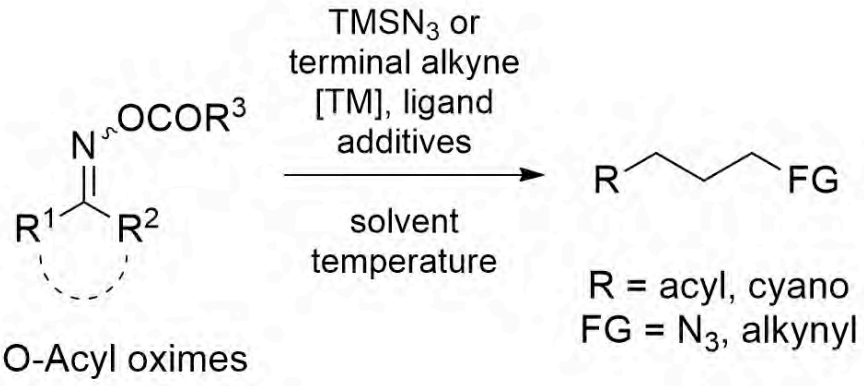
[1] Matthieu Tissot, Nathalie Body, Sylvain Petit, Jehan Claessens, Christophe Genicot, Patrick Pasau, *Organic Letters.* **2018**, *20*, 8022
[2] Matthieu Tissot, Jérome Jacq, Patrick Pasau, *Organic Process Research Development* **2019**, *asap*

Remote C(sp^3)-H Functionalization Enabled by Transition Metals

R. O. Torres-Ochoa[1], A. Leclair[2], Z. Li[3], Q. Wang[2], J. Zhu[2]*

[1]Departamento de Química Orgánica, Instituto de Química, Universidad Nacional Autónoma de México, [2]Laboratory of Synthesis and Natural Products, ISIC, EPFL Lausanne, [3]College of Material and Energy, South China Agricultural University

C(sp^3)-H bond functionalization represents the most direct and desirable synthetic strategy to create new C-C/C-X (heteroatom) bonds.[1] The main obstacles that hamper the growth of such a field concern to the extremely low reactivity of C-H bonds together with its widespread ubiquity in organic molecules, which brings regioselectivity issues. The use of nitrogen centered radicals (NCR) as synthetic intermediates[2] has lighted the way to overcome such difficulties due to their high reactivity and notable tendency to evolve into a carbon center radical.[3] The development of new synthetic procedures that allow the formation of NCR in a much milder fashion has tremendously contributed to their resurgent and exploitation in the C(sp^3)-H bond functionalization research area. For instance, iminyl radicals can be smoothly formed via N-O cleavage of hydroxylamine derivatives[4] by transition metals,[5] and their subsequent regioselective progression into a C(sp^3)-centered radical, via either scission of the ring-strained NCR intermediate,[6] or 1,5-hydrogen atom transfer (HAT)[7], provides the opportunity to incorporate new functionalities on distal and initially unreactive positions. Based on the reactivity of those NCR, we developed a set of transformations that allowed us to create C(sp^3)-N and C(sp^3)-C(sp) bonds in remote positions of ketones and nitriles by using easily accessible O-acyl oximes as starting materials.



[1] a) Hong Yi, Guoting Zhang, Huamin Wang, Zhiyuan Huang, Jue Wang, Atul K. Singh, Aiwen Lei, *Chem. Rev.***2017**, 117, 9016-9085; b) Yan Qin, Lihui Zhu, Sanzhong Luo, *Chem. Rev.* **2017**, 117, 9433-9520; c) Heiko Sommer, Francisco Juliá-Hernández, Ruben Martin, Ilan Marek,*ACS Cent. Sci.* **2018**, 4, 153-165.
[2] Samir Z. Zard, *Chem. Soc. Rev.* **2008**, 37, 1603-1618.
[3] Shunsuke Chiba, Hui Chen, *Org. Biomol. Chem.* **2014**, 12, 4051-4060.
[4] a) John C. Walton, *Acc. Chem. Res.* **2014**, 47, 1406-1416; b) John C. Walton, *Molecules*, **2016**, 21, 63; c) Huawen Huang, Jinhui Cai, Guo-Jun Deng, *Org. Biomol. Chem.* **2016**, 14, 1519-1530.
[5] Mitsuru Kitamura, Koichi Narasaka, *Chem. Pharm. Bull. Jpn.* **2008**, 81, 539-547.
[6] Wenqing Yin, Xuelian Wang, *New J. Chem.* **2019**, 43, 3254-3264.
[7] Jacob Davies, Sara P. Morcillo, James J. Douglas, Daniele Leonori, *Chem. Eur. J.* **2018**, 24, 12154-12163.

Assessment of the Synthetic Feasibility of Generated Chemical Space by Computer Assisted Synthesis Planning

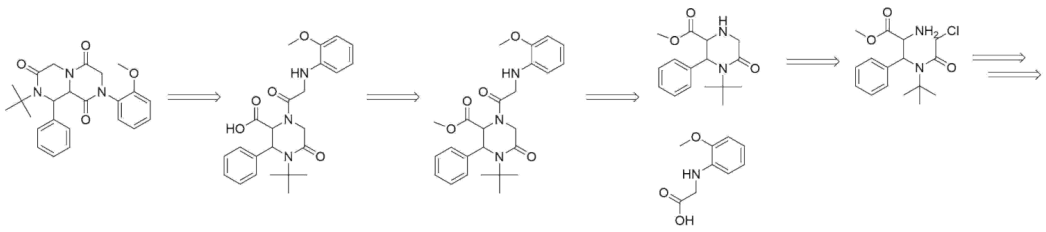
A. Thakkar[1], V. Chadimova[2], E. J. Bjerrum[2], O. Engkvist[2], J. L. Reymond[1]*

[1]Department of Chemistry and Biochemistry, Freiestrasse 3, 3012 Bern, [2]Hit Discovery, Discovery Sciences, R&D, AstraZeneca, Gothenburg, Sweden

Computer assisted synthesis planning has gained considerable interest in recent years owing to the resurgence of artificial intelligence (AI), and the prospect of accelerating the discovery and synthesis of new chemical entities.[1] Our previous work highlights the implementation of a retrosynthetic prediction tool trained on the largest collection of datasets to date, and demonstrates its applicability to a set of compounds obtained from virtual libraries.[2] Additionally, we have further augmented our CASP tool with a model called 'Ring Breaker' to assess synthetic disconnections for complex ring systems.[3] This model is trained specifically for ring forming reactions and is used to augment the search for synthetic pathways by identifying routes that utilise ring formations. To maximise the number of synthetic options during the search for synthetic pathways, we further augment the model with an applicability filter, which informs the model which reactions are applicable *in silico*.

In this study, we build upon our previous work in computer aided synthesis planning (CASP) by tackling the problem of synthetic accessibility.[2, 3] The improvements to our baseline retrosynthetic tool allow for a better estimation of the synthetic feasibility of a diverse set of compounds obtained from ChEMBL, GDBChEMBL, GDBMedChem and Drugbank, as determined by running full retrosynthetic predictions. The outcomes of the retrosynthetic predictions are used as an estimate for synthetic feasibility and are used to train a variety of machine/deep learning models that can be used as a surrogate to the prediction of full synthetic routes. The resulting surrogate model can be used to score the synthetic accessibility of a diverse set of generated compounds from virtual libraries or used in the generation process to maximise the synthetic feasibility of compounds.

AI generated route for the bicyclic piperazine



[1] Jensen, K. F.; Coley, C. W.; Eyke, N. S., Autonomous discovery in the chemical sciences part I: Progress. *Angewandte Chemie International Edition* **2019**.
[2] Thakkar, A.; Kogej, T.; Reymond, J.-L.; Engkvist, O.; Bjerrum, E. J., Datasets and their influence on the development of computer assisted synthesis planning tools in the pharmaceutical domain. *Chemical Science* **2020,** *11* (1), 154-168.
[3] Thakkar, A.; Selmi, N.; Reymond, J.-L.; Engkvist, O.; Bjerrum, E. J., 'Ring Breaker': Neural Network Driven Synthesis Prediction of the Ring System Chemical Space. *ChemRxiv* **2020**.

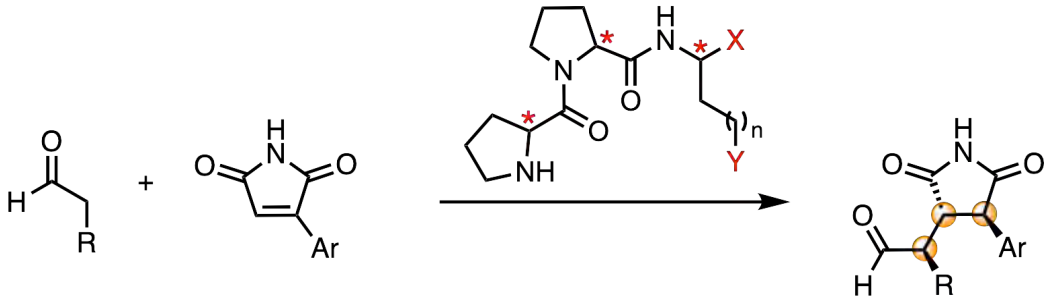
Catalytically Active Peptides For Conjugate Addition Reactions with *C*-substituted Maleimides

G. Vastakaite[1], H. Wennemers[1]*

[1]Laboratory of Organic Chemistry, D-CHAB, ETH Zürich

Peptides of the type H-Pro-Pro-Xaa (Xaa = any amino acid) are highly reactive and stereoselective catalysts for organocatalytic C-C bond formations, such as aldol reactions[1] as well as conjugate addition reactions of aldehydes to nitroolefins[2] and maleimides.[3]

The poster will focus on the expansion of the scope of peptide catalyzed conjugate addition reactions to a reaction that provides products with 3 contiguous stereogenic centres. We show that the reaction proceeds with high regio- and chemoselectivity and without major side reactions of the unprotected maleimides. We also present insights into the reaction mechanism.



[1] P. Krattiger, R. Kovasy, J. D. Revell, S. Ivan, H. Wennemers, *Org. Lett.* **2005**, 7, 6, 1101.
[2] a) M. Wiesner, M. Neuburger, H. Wennemers, *Chem. Eur. J.* **2009**, 15, 10103. b) J. Duschmalé, H. Wennemers, *Chem. Eur. J.* **2012**, 18, 1111. c) T. Schnitzer, A. Budinska, H. Wennemers, *Nature Catalysis* **2020**, 3, 143.
[3] C. Grünenfelder, J. Kisunzu, H. Wennemers, *Angew. Chem. Int. Ed.* **2016**, 55, 8571.

Thermal and Electrical Transport Through Organic Radicals: Taking Advantage of the Kondo Effect

D. Vogel[1], C. Hsu[2], M. Mayor[1,3]*, H. van der Zant [2]*

[1]University of Basel, Department of Chemistry, [2]Delft University of Technology, Kavli Institute of Nanoscience, [3]Karlsruhe Institute of Technology (KIT), Institute for Nanotechnology (INT)

The Kondo effect predicts an increase in conductivity if the conducting electrons pass by a spin impurity situated on an organic molecule or quantum dot between two electrodes at low temperatures. This zero-bias anomaly in the low temperature regime is of interest for electrical and thermal conductivity through organic molecules. Therefore we have designed and synthesized several stable organic radicals, which are comprised of an aryl backbone functionalized with two pyridine anchoring groups and a nitronyl-nitroxide based radical. The influence of the relative position of the anchoring groups to the radical was studied and first results will be presented on the following poster. These preliminary results suggest that close proximity of the anchoring group to the radical increases the Kondo effect.

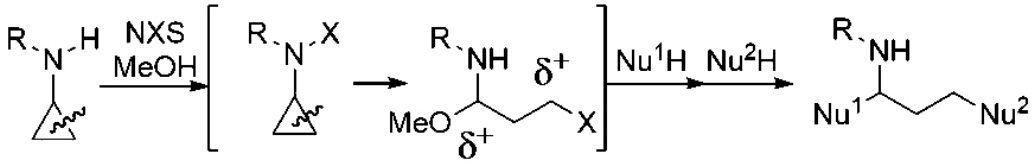
Oxidative ring-opening fluorination of cyclopropylamides

M. Wang[1], J. Waser[1]*

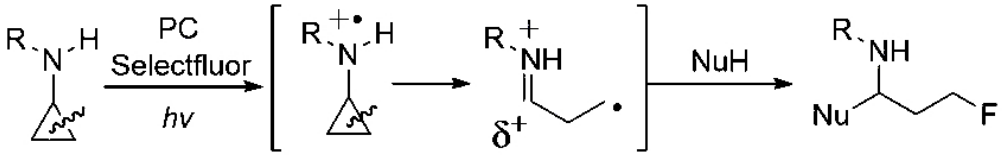
[1]Laboratory of Catalysis and Organic Synthesis (LCSO), Institute of Chemical Sciences and Engineering (ISIC), EPFL

Aminocyclopropanes are important building blocks in synthetic chemistry. Their reactivity was explored mainly by utilizing transition-metal catalysis to form a metallocyclobutane intermediates, or by photoredox chemistry to oxidize the amino group to a radical cation species.[1] Our group has focused in the past on the ability of donor-acceptor substituted aminocyclopropanes (D-A aminocyclopropanes) to react as zwitterionic synthons [2] and recently, we reported a different strategy for the activation of mono-substituted aminocyclopropanes giving access to biscationic synthons (Figure 1A). [3]

A. Our previous work: 1,3-difunctionalization of aminocyclopropanes



B. This work: ring-opening fluorination of cyclopropylamides



We herein reported a mild ring-opening fluorination of cyclopropylamides enabled by photoredox catalysis (Figure 1B). The amide nitrogen was oxidized to form a radical cation species which induced ring opening fluorination by reacting with F^+ source like SelectFluor. Introducing a series of nucleophiles to the imine carbon center can be done under acidic conditions, thus generating a wide range of 3-fluorinated propylamides in one pot.

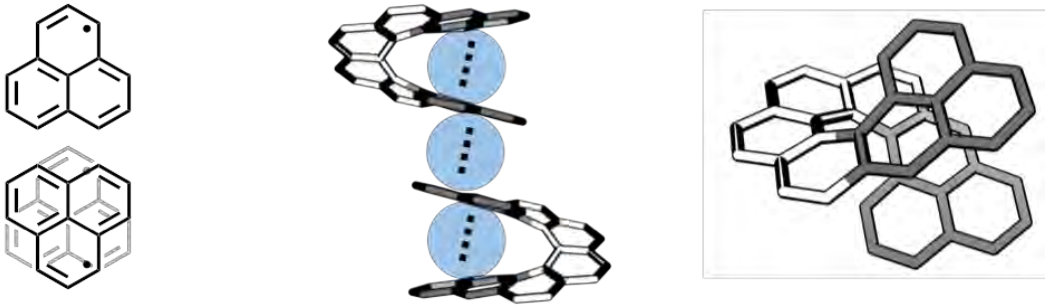
[1] Rassadin, V. A.; Six, Y. *Tetrahedron* **2016**, *72*, 4701-4757.
[2] a) F. de Nanteuil, F. De Simone, R. Frei, F. Benfatti, E. Serrano, J. Waser, *Chem. Commun.* **2014**, *50*, 10912-10928; b) S. Racine, B, Hegedus, R. Scopelliti, J. Waser, *Chem. Eur. J.* **2016**, *22*, 11997-12001; c) J. Preindl, S, Chakrabarty, J. Waser, *Chem. Sci.* **2017**, *8*, 7112-7118; d) D. Perrotta, M.-M. Wang, J. Waser, *Angew. Chem. Int. Ed.* **2018**, *57*, 5120-5123.
[3] M.-M. Wang, J. Waser, *Angew. Chem. Int. Ed.* **2019**, *58*, 13880-13884.

Cethrenes: Self-assembly of magnetic conducting molecular wires

Y. Wang[1]

[1]University of Zurich, Department of Chemistry

Molecular wires may one day replace metal- and silicon-based wires in electronic devices. One possibility for making such wires is self-assembly of conjugated organic molecules with the aid of π–π stacking or van der Waals interactions. Our approach for the assembly of molecules into wires employs a multi-center bonding interaction, known as pancake bond. This bonding motif, which enhances charge transport in bulk materials, is typical for spin-delocalized conjugated systems. An example of such systems is phenalenyl radical,[1] in which one unpaired electron is uniformly delocalized between six carbon atoms. Due to the presence of the unpaired electron, phenalenyl exists in equilibrium with its sigma-dimer.[2] When the formation of the sigma-dimer is suppressed kinetically, a pi-dimer forms instead via a two-electron multi-center covalent bond[3] (Figure 1, left). Fusing of two phenalenyl units via a helical backbone results in molecules named cethrenes, in which electrons can communicate through backbone and space simultanously.[4] The predisposition for pancake bonding makes cethrenes good candidates for self-assembled materials (Figure 1, middle). The objective of this research was to synthesize cethrene composed of ten benzenoid rings that contains two unpaired electrons (Figure 1, right) and study its self-assembly into helical wires. This system will allow us to study the effect of intramolecular spin-interaction on the intermolecular one and to establish design principles of self-assembly of spin-delocalized systems and, ultimately, magnetic conducting materials.



[1] D. H. Reid, *Q. Rev. Chem. Soc.* **1965**, 19, 274–302.
[2] Z. Mou, K. Uchida, T. Kubo, M. Kertesz, *J. Am. Chem. Soc.* **2014**, 136, 18009–18022.
[3] K. Goto, T. Kubo, K. Yamamoto, K. Nakasuji, K. Sato, D. Shiomi, T. Takui, M. Kubota, T. Kobayashi, K. Yakusi, J. Y. Ouyang, *J. Am. Chem. Soc.* **1999**, 121, 1619–1620.
[4] P. Ravat, T. Šolomek, M. Rickhaus, D. Häussinger, M. Neuburger, M. Baumgarten, M. Juríček, *Angew. Chem. Int. Ed.* **2016**, 55, 1183–1186.

Synthesis of Carpyridines

J. F. Woods[1], M. Rickhaus[2]*

[1]Department of Chemistry, University of Zurich, [2]Department of Chemistry, University of Zürich

Porphyrins are a well-researched class of aromatic chromophores due to their range of uses as ligands in biology and roles in larger supramolecular structures,[1,2] as well as their electronic and optical properties.[3] A largely unexplored but related construct are macrocycles composed of pyridine and carbazole subunits, initially reported by Müllen,[4] which we term ‘carpyridine’.

The inclusion of two oppositely facing five membered rings in the carbazole moiety allows carpyridines to exhibit a negative curvature, which is confirmed by crystallography.[4] Despite bending within the macrocycle, the cavity still provides a vacancy for chelation to a metal adopting a square planar geometry. Unoccupied axial sites of a coordinated metal present an opportunity for metal-metal interactions with other monomers to take place such that a relay of communication may occur between units and should be evident upon inspection of optical properties.

Several first-row transition metals have been successfully coordinated into the related ‘carpyzin’ (pyridine moiety replaced by pyrazine) through use of microwave radiation and have a stark effect upon the photochemical properties of the system (Figure 1). Modification of carpyridine side chains will also alter the behaviour of the monomers, and in turn, an effect is had upon the optical properties. Bulky, branched groups (R = *t*Bu) will prevent aggregation due to steric crowding whereas linear alkyl chains (R = *n*-$C_{12}H_{25}$) promote association and may lead to aggregation induced emission in the absence of a metal or quenching in the inclusion of one.

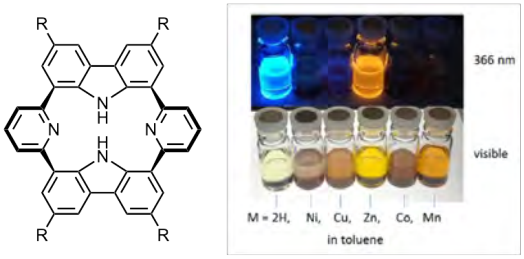


Figure 1. Carpyridine monomer, left, and coordinated metals into carpyzins, right.

Modification of carpyridine side chains will also alter the behaviour of the monomers, and in turn, an effect is had upon the optical properties. Bulky, branched groups (R = tBu) will prevent aggregation due to steric crowding whereas linear alkyl chains (R = *n*-$C_{12}H_{25}$) promote association and may lead to aggregation induced emission in the absence of a metal or quenching in the inclusion of one.

[1] F. N. Liew, M. A. Brandys, S. Biswas, J. N. Nguyen, M. Rahmawati, M. Nevala, B. O. Elmore, M. P. Hendrich, H. J. Kim, Biochemistry, 2020, 59, 704.
[2] M. Rickhaus, M. Jirasek, L. Tejerina, H. Gotfredsen, M. D. Peeks, R. Haver, H. W. Jiang, T. D. W. Claridge, H. L. Anderson, Nature Chemistry, 2020, 12, 236.
[3] A. Khadria, J. Fleischhauer, I. Boczarow, J. D. Wilkinson, M. M. Kohl, H. L. Anderson, iScience, 2018, 4, 153.
[4] L. Arnold, H. Norouzi-Arasi, M. Wagner, V. Enkelmann, K. Müllen, Chem. Commun., 2011, 47, 970.

Access to *P*- and Axially Chiral Biaryl Phosphine Oxides by Enantioselective Cp^xIr^{III}-Catalyzed C-H Arylations

Ł. Woźniak[1], Y. S. Jang[1], J. Pedroni[1], N. Cramer[1]*

[1]Laboratory of Asymmetric Catalysis and Synthesis, EPFL Lausanne

Chiral biaryl phosphine ligands are a critically important cornerstone of asymmetric transition-metal catalysis. [1] Chiral elements such as a stable chiral axis of the binaphthyl backbone or a *P*-chiral center are key structural features. A combination of these two elements has proven advantageous for a few catalytic transformations. [2,3] However, harnessing the full potential of ligands possessing both a chiral axis and a *P*-chiral phosphorus atom is often hampered by their elaborate multistep synthesis. [4]

Herein, we present a methodology for the synthesis of *P*- and atrop-chiral biaryl phosphine oxides by highly asymmetric iridium catalyzed C-H arylation of phosphine oxides with *o*-quinone diazides. [5] The subsequent enantiospecific reductions provide monodentate chiral phosphorus(III) compounds having structures with proven importance as ligands in asymmetric catalysis. The cooperative action of the iridium(III) complex bearing an atropchiral cyclopentadienyl (Cp^x) ligand [6] and phthaloyl *tert*-leucine cocatalyst enables enantioselective C-H arylation. This method allows a) access to *P*-chiral biaryl phosphine oxides, b) atropo-enantioselective construction of sterically demanding biaryl backbones, and also c) selective assembly of axial and *P*-chiral compounds in excellent yields and diastereo- and enantioselectivities.

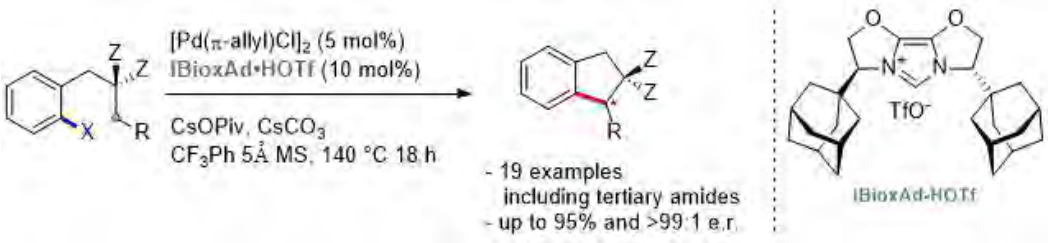
[1] Privileged Chiral Ligands and Catalysts (Eds.: Q.-L. Zhou), Wiley-VCH, Weinheim, **2011**.
[2] A. M. Taylor, R. A. Altman, S. L. Buchwald, *J. Am. Chem. Soc*. **2009**, *131*, 9900-9901.
[3] S. Rousseaux, J. Garcia-Fortanet, M. A. Del Aguila Sanchez, S. L. Buchwald,*J. Am. Chem. Soc*. **2011**, *133*, 9282-9285.
[4] T. Hamada, S. L. Buchwald, *Org. Lett*. **2002**, *4,* 999-1001.
[5] Y.-S. Jang, Ł. Woźniak, J. Pedroni, N. Cramer, *Angew. Chem. Int. Ed*. **2018**, *57*, 12901-1290.
[6] C. G. Newton, D. Kossler, N. Cramer, *J. Am. Chem. Soc*. **2016**, *138*, 3935-3941.

Pd^0-catalyzed Enantioselective Intramolecular Arylation of Enantiotopic Secondary C–H Bonds

M. Zuccarello[1], R. Melot[1], D. Cavalli[1], N. E. Niggli[1], O. Baudoin[1]*

[1]Department of Chemistry, University of Basel, Switzerland

Enantioselective C–H activation is a current topic of high interest providing access to structures of great complexity from easily accessible precursors in a step economical manner. Despite efforts from the Cramer, Kündig, Kagan and our group in asymmetric Pd^0-catalyzed C–H activation, methods where the stereogenic center is formed at the activated site remain scarce.[1,2] The synthesis of β-lactams by activation of benzylic C(sp^3)–H bonds by Cramer remains the only example to this date.[3] Herein, we report the highly enantioselective synthesis of indanes using IBiox-type NHC[4,5] ligands.[7]



High yields (up to 95%) and enantioselectivies (e.r. up to >99:1) were obtained across a variety of products. The reaction tolerates a wide range of substituents including electron donating and withdrawing groups on the aromatic part and different functionalities on the chain undergoing C-H activation. Additionally, the synthesis of tertiary amides with a labile stereocenter could be achieved without any drop in enantioselectivity.

[1] C. G. Newton, S. G. Wang, C. C. Oliveira, N. Cramer, *Chem. Rev.* **2017**, *117*, 8908–8976.
[2] T. G. Saint-Denis, R.-Y Zhu, G. Chen, Q.-F Wu, J.-Q Yu, *Science* **2018**, *359*, 759–770.
[3] J. Pedroni, M. Boghi, T. Saget, N. Cramer, *Angew. Chem. Int. Ed*. 2014, *53*, 9064–9067.
[4] F. Glorius, G. Altenhoff, R. Goddard, C. W. Lehmann, *Chem. Commun.* **2002**, 2704–2705.
[5] S. Würtz, C. Lohre, R. Fröhlich, K. Bergander, F. Glorius, *J. Am. Chem. Soc.* **2009**, *131*, 8344–8345.
[7] R. Melot, M. Zuccarello, D. Cavalli, N. Niggli, M. Devereux, O. Baudoin, submitted work.