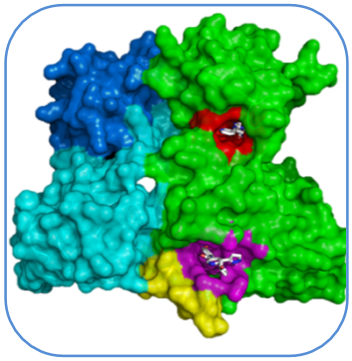
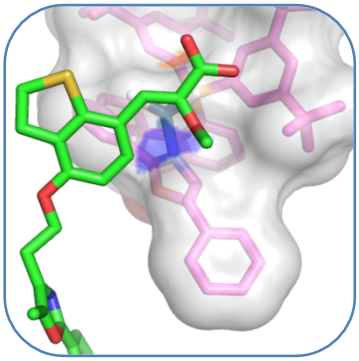
Swiss Chemical Society (SCS)

1st Swiss Industrial Chemistry Symposium SICS'16

October 28, 2016, 08.30 - 18.00
University of Basel
Grosser Hörsaal OC, St. Johanns-Ring 19


Swiss Chemical Society (SCS)
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Program Morning Session

08.30	Welcome coffee, registration
08.55	Opening, welcome
09.00	Dr. Andreas Marzinzik, Novartis Pharma AG *«Towards the goal of curing CML: discovery of ABL001 a novel allosteric inhibitor of BCR-ABL preventing disease relapse by dual targeting»*
09.30	Dr. Kurt Püntener, F. Hoffmann-La Roche AG *«With asymmetric hydrogenation towards scalable, stereoselective syntheses of Aleglitazar and Bitopertin»*
10.00	Dr. Ulla Létinois, DSM Nutritional Products AG *«Bio-based aromatic building blocks for vitamin E manufacture»*
10.30	*Coffee Break*
11.00	Dr. Cheng-yi Chen, Janssen R&D, Cilag AG *«A Synthesis of 1H-Indazoles via a $Cu(OAc)_2$-catalyzed N-N Bond Formation»*
11.30	4x Short Talks à 8min Dr. Kai-Uwe Schöning, BASF Schweiz AG *«Hindered amine polymer stabilizers – new discoveries in an established research area»* Dr. Alec Birkbeck, Firmenich SA *«From Leopold Ruzicka in 1935 until now: the story of (Z)-β-Santalol at Firmenich, towards an industrial synthesis»* Dr. Corinna Nimphius, Clariant International Ltd *«Glucamides – a new platform of sugar-based surfactants»* Dr. Wolfgang Haap, F. Hoffmann-La Roche AG *«Discovery of the cathepsin S inhibitor RG7625 for the treatment of autoimmune diseases»*

Lunch and Poster Sessions

12.10	*Lunch buffet*
12.45	Poster session A and coffee (2nd and 3rd floor)
13.15	Poster session B and coffee (2nd and 3rd floor)

Program Afternoon Session

14.00	4x Short Talks à 8min Dr. Myriem El Qacemi, Syngenta Crop Protection AG *«Enantioselective synthesis of insecticidal isothiazolines»* Dr. Fabrice Gallou, Novartis Pharma AG *«Alternative solvents: from a compliance-driven activity to a trigger for innovation»* Dr. Johannes Schranck, Solvias AG *«Catalysis @ Solvias – from science to business»* Dr. Christian Lothschütz, Siegfried AG, Zofingen *«What can academia learn from industry?»*
14.45	Dr. Stefan Abele, Actelion Pharmaceuticals Ltd. *«Pilot plant production of a $P2Y_{12}$-antagonist containing (R)-3-Phosphonoalanine»*
15.15	Dr. Christoph Taeschler, Lonza AG «Process development aspects of alkylnitrites»
15.45	*Coffee Break*
16.15	Dr. Rolf Schaller, Dottikon Exclusive Synthesis AG *«Advanced process development into future»*
16.45	Panel discussion with the lecturers
17.20	*Award ceremony for the best poster presentation*
17.30	*Aperitif and Networking*

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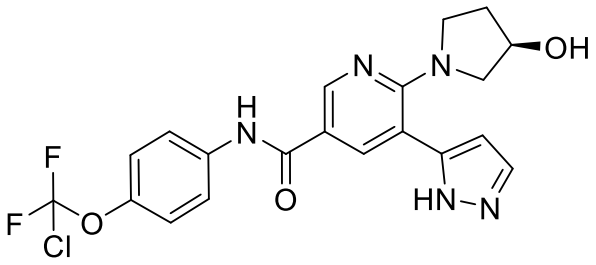
Abstracts of Lectures and Short Talks

Towards the goal of curing CML: discovery of ABL001 a novel allosteric inhibitor of BCR-ABL preventing disease relapse by dual targeting

Andreas Marzinzik,* Xavier Pellé, Robert Grotzfeld, Joseph Schoepfer, Giuliano Berellini, Hongbo Cai, Giorgio Caravatti, Pascal Furet, A. Quamrul Hassan, Tami Hood, Sandra Jacob, Alice Loo, Paul Manley, Bahaa Salem, Sreenath Sharma, Wenjing Zhu, Gary Vanasse, Andrew Wylie, Wolfgang Jahnke

*Novartis Institutes for Biomedical Research, Forum 1, Novartis Campus, CH - 4056 Basel, andreas.marzinzik@novartis.com

The discovery of ABL001, the first allosteric selective receptor tyrosine kinase inhibitor in Phase I clinical trial for the treatment of patients with chronic myelogenous leukemia (CML) and a subset of acute lymphoblastic leukemia (ALL) will be reported. Two aspects of this ground breaking discovery have significant impacts on cancer research. Firstly; ABL001 is a potent BCR-ABL inhibitor with a novel, allosteric mechanism of action. In contrast to inhibitors such as imatinib and nilotinib that bind to the ATP-site of the kinase domain ABL001 binds to a distinct allosteric site on the kinase domain. Secondly this presents a unique opportunity to treat patients with Ph+ leukemia using a combination of two potent, mechanistically distinct BCR-ABL inhibitors. Pre-clinical efficacy studies have illustrated the potential of this approach with complete regressions being achieved in animals receiving an ABL001/nilotinib combination with no evidence of disease relapse despite treatment being withdrawn. A similar combination approach in the clinic would be anticipated to provide patients with a deeper and more sustained reduction in tumor burden with a reduced risk of relapse. Achieving such a goal would be an important step towards the next paradigm shift providing a cure for patients with CML.



ABL001

Low molecular weight compounds previously identified to bind to the myristoyl-pocket of BCR-ABL, failed to progress to clinical candidates. To develop superior starting points for medicinal chemistry we performed fragment-based screens and the resulting hits were optimized using in silico docking, crystallography and NMR studies. We discovered that myristoyl-pocket binders must induce a critical "bend" in the C-terminal helix for the kinase to form the auto-inhibited conformation.[1] Small molecule medicinal chemistry starting points were discovered using a NMR conformation assay confirming that the molecules could bend the helix. Furthermore the structure-based optimization to improve potency, selectivity and in vivo pharmacokinetics, leading to the discovery of ABL001 will be reported. We will discuss how combinations of ABL001 with the ATP-competitive inhibitor nilotinib, prevents the emergence of drug resistance in vivo. Clinical testing of ABL001 in combination with catalytic-site inhibitors is underway to determine if the pre-clinical observations translate to the clinic and provide potentially curative treatment regimens for patients.

[1] W. Jahnke, R. M. Grotzfeld, X. Pelle, A. Strauss, G. Fendrich, S.W. Cowan-Jacob, S. Cotesta, D. Fabbro, P. Furet, J. Mestan, A. L. Marzinzik, *J. Am. Chem. Soc.* **2010**, 132, 7043-7048.

With asymmetric hydrogenation towards a scalable, stereoselective syntheses of Aleglitazar and Bitopertin

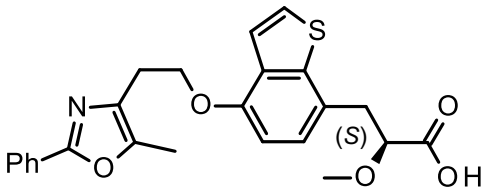
Kurt Püntener

F. Hoffmann-La Roche Ltd, Pharmaceuticals Division
Roche Innovation Center Basel
preclinical CMC Process Reserach, CH-4070 Basel, Switzerland

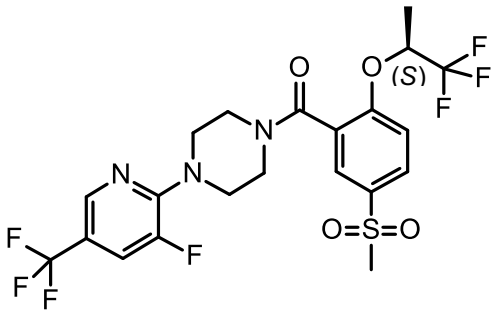
In recent years new drug candidates containing one or more chiral centers are developed almost exclusively as pure enantiomers. Their increasing structural complexity together with the public pressure on drug pricing has made cost of goods a critical issue. In this context, the task of a synthesis & process research chemist is to find shorter synthetic routes in which the chiral centers are directly and selectively established in the desired configuration in order to avoid labor- and equipment-intensive resolution processes, as well as to develop the synthesis in the limited time frame available.

The presentation gives an insight into the role of Roche's Process Research & Catalysis units in the development of new drugs. In the first part of the presentation, the process towards the potential commercial API route, started with the optimization of the existing Medicinal Chemistry route and concluded with the creation of an entirely new route, will be exemplified with Roche's dual PPAR agonist Aleglitazar. Particularly, the stereoselective synthesis of (2S)-alkoxy propionic acids via Lewis acid-mediated diastereoselective aldol reaction and asymmetric (transfer) hydrogenation will be presented.

In the second part of the presentation, the enantioselective hydrogenation of 1,1,1-trifluoroacetone to (S)-1,1,1-trifluoro-2-propanol - key building block in Bitopertin - will be highlighted. The relevant criteria associated with the application of the asymmetric hydrogenation technology will be addressed, such as the activity, the selectivity and the accessibility of the catalysts, as well as of the availability and the quality of hydrogenation substrates. Successful laboratory and pilot plant campaigns will be described.



Aleglitazar



Bitopertin

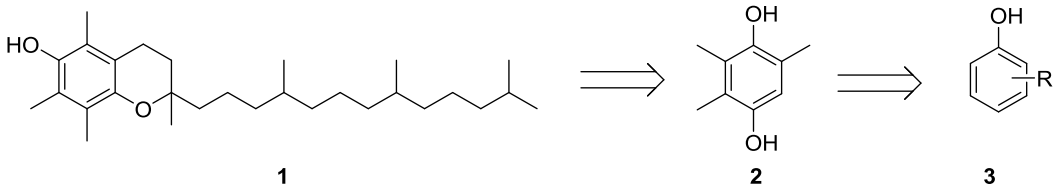
Bio-Based Aromatic Building Blocks for Vitamin E Manufacture

Ulla Létinois, Thomas Netscher, Werner Bonrath

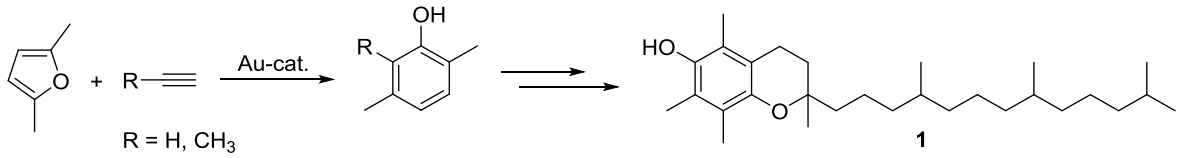
Research and Development, DSM Nutritional Products,
P.O. Box 2676, 4002 Basel, Switzerland; ulla.letinois@dsm.com

Strategies for mitigation of greenhouse gas emissions include significant reduction of fossil resource consumption in the field of energy supply and chemical production. In chemical industry more environmentally friendly manufacturing alternatives are therefore required.

Synthetic vitamin E, the industrially most important antioxidant for feed, food and pharma applications, is currently produced from the fossil resources m-cresol, acetylene, methanol and acetone[1] on a scale of >30'000 tons per year worldwide. For manufacture of **1** via 2,3,5-trimethylhydroquinone (**2**) we were interested in phenols (**3**) from renewable resources[2] having an appropriate substitution pattern.



Hashmi's gold-catalyzed furan-yne-cycloisomerization reaction[3] starts from furans which are available from renewable resources[4] and yield phenols. We reasoned that intermolecular reactions between 2,5-dimethylfuran and small, gaseous alkynes should give access to desired dimethyl or trimethyl phenols. To the best of our knowledge, no such bio-based route to aromatic building blocks for vitamin E synthesis was known so far.



In the present contribution, the new synthesis of α-tocopherol based on the key transformation of furans with acetylene and propyne will be discussed[5] as well as the determination of the eco footprint for both processes.

[1] M. Eggersdorfer, D. Laudert, U. Létinois, T. McClymont, J. Medlock, T. Netscher, W. Bonrath, *Angew. Chem. Int. Ed.* **2012**, *51*, 12960–12990.
[2] E. de Jong, A. Higson, P. Walsh, M. Wellisch, International Energy Agency, Report IEA Bioenergy Task 42, **2012.**
[3] A. Zeiler, M. J. Ziegler, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Adv. Synth. Catal.* **2015**, *357*, 1507–1514 and references cited therein.
[4] Y. Román-Leshkov, C. J. Barrett, Z. Y. Liu, J. A. Dumesic, *Nature* **2007**, *447*, 982–985.
[5] W. Bonrath, U. Letinois, T. Netscher, *WO 2015110655*, **2015**; W. Bonrath, U. Letinois, T. Netscher, *WO 2015110654*, **2015**.

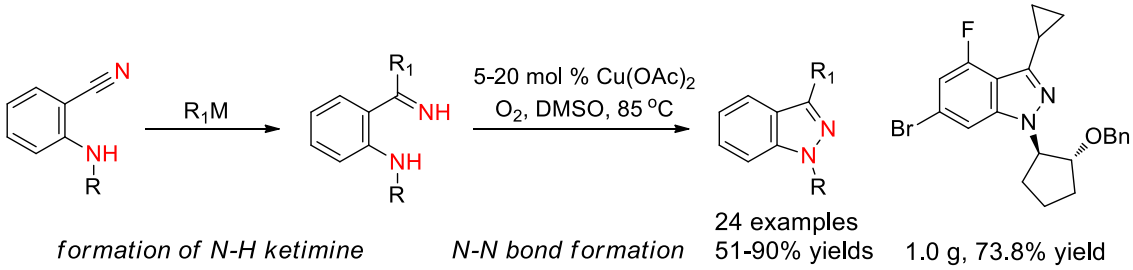
A Synthesis of 1*H*-Indazoles *via* a $Cu(OAc)_2$-catalyzed N-N Bond Formation

Cheng-yi Chen,[*,†] Guangrong Tang,[‡] Fengxian He,[‡] Zhaobin Wang,[‡] Hailin Jing[‡] and Roger Faessler[†]

[†]Janssen R&D, Pharmaceutical Development and Manufacturing Sciences, Small Molecule API Switzerland, Cilag AG, Hochstrasse 201, 8205 Schaffhausen, Switzerland

[‡]Porton (Shanghai) R&D Center, 1299 Ziyue Road, Zizhu Science Park, Minhang District, Shanghai 200241, China

A facile synthesis of 1*H*-indazoles featuring a $Cu(OAc)_2$-catalyzed N-N bond formation using oxygen as the terminal oxidant is described. The reaction of readily available 2-aminobenzonitriles with various organometallic reagents led to *ortho*-aminoaryl N-H ketimine species. The subsequent $Cu(OAc)_2$-catalyzed N-N bond formation in DMSO under oxygen afforded a wide variety of 1*H*-indazoles in good to excellent yields.



[1] C.-y. Chen, G. Tang, F. He, Z. Wang, H. Jing, R. Faessler, *Org. Lett.*, **2016**, *18*, 1690-1693.

Hindered Amine Polymer Stabilizers – new discoveries in an established research area

Kai-Uwe Schöning

Senior scientist R&D, BASF Schweiz AG
kai-uwe.schoening@basf.com

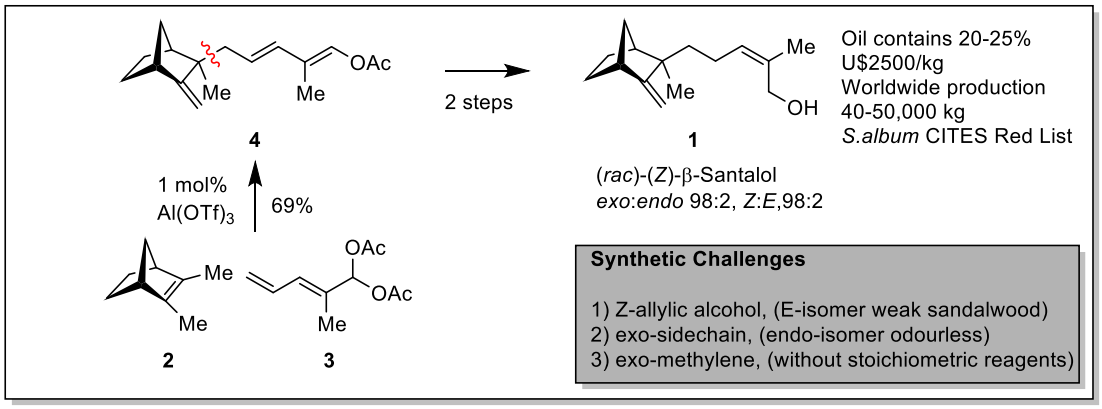
Hindered amine polymer stabilizers represent an important research area within the large field of polymer additives. This is particularly true for the class of so-called N-alkoxy-tetramethylpiperidines. This lecture will present recent efforts toward the formation of N-O-alkyl moieties.

From Leopold Ruzicka in 1935 until now: The Story of (*Z*)-β-Santalol at Firmenich:- Towards an Industrial Synthesis.

Alec Birkbeck

(Synthesis and Pilot Plant, Corporate R&D, Firmenich *SA*. PO Box 239, 1211-Geneva 8, Switzerland.)

The original structural determination of β-Santalol **1** by Leopold Ruzicka in 1935 spurred a long term interest at Firmenich, in both the constituents of East Indian Sandalwood Oil and synthetic substitutes for this highly prized essential oil.[1] Over the last 40 years, the ever dwindling supply and increasing price of East Indian Sandalwood oil has stimulated extensive research towards both an economical and scalable synthesis of (-)-(*Z*)-β-Santalol **1**, present at 20-25% in the essential oil and largely responsible for its typical, lactonic sandalwood odour.[2] Steam distillation of East Indian Sandalwood (*S.album L.*) gives the essential oil in yields of 5-7%; that oil now fetches *ca*. U$2,500/kg with an annual worldwide production of 40-50,000 kg. Other isomers present in the oil contribute little to the odour and the (+) enantiomer is odourless, placing challenging demands on the precise stereochemical control of any synthesis. **Figure 1.**[3]



Despite many elegant academic syntheses and industrial efforts, to date, no industrially feasible synthesis of (*Z*)-β-Santalol **1** has been realised on large scale.[4] We herein describe the discovery of a novel coupling reaction between santene **2** and allylidene diacetate **3** giving the key dienol acetate intermediate **4** in one step. Subsequent 1,4 hydrogenation and acetate ester removal furnished *rac*-(*Z*)-β-Santalol **1** in good overall yield, which is not only the shortest synthesis to date but all reactions are economical and scalable. This new synthesis employs an unprecedented coupling reaction and 2 further catalytic transformations with only one redox manipulation necessary to install the pivotal (*Z*)-allylic alcohol.

[1] L. Ruzicka and G. Thomman, *Helv. Chim. Acta* **1935**, *18*, 355. E. Demole, C. Demole and P. Enggist, *Helv. Chim. Acta* **1976**, *59*, 737. C. Chapuis, *Chem. Biodiversity* **2004**, *1*, 980.

[2] E-J. Brunke and G. Schmaus, *Dragoco Report*, **1995**, *42*, 195, 245.

[3] G. Helmchen and A. Krotz, *Tet. Asymm*., **1990**, *1*, 537.

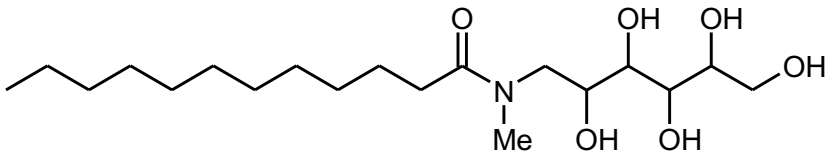
[4] A.A. Birkbeck, X. Marquet, P. Millet and H. Pamingle, *Eur. J. Org Chem*., **2014**, *34*, 7582. C. Fehr, I. Magpantay, M. Vuagnoux and P. Dupau, *Chem. Eur. J*., **2011**, *17*, 1257. and references cited therein.

Glucamides – A new platform of sugar-based Surfactants

Corinna Nimphius, Franz Xaver Scherl, Klaus Raab, Peter Klug

Clariant International Ltd, Hardstraße 61, 4133 Pratteln, Switzerland;
Clariant Produkte (Deutschland) GmbH, Industrieparkstraße 1, 84508 Burgkirchen, Germany,
corinna.nimphius@clariant.com

The global consumer market trends - Convenience, Well-Being, Economy and Sustainability - are key triggers for new surfactant developments. In line with its strategic pillars "Foster Innovation and R&D" and "Add value with Sustainability" Clariant has developed a new range of Glucamide surfactants which deliver outstanding performance profiles. Glucamides are well known since many years, but did not find broad application in the past mainly due to lack of commercial availability. Nowadays Clariant's Glucamides offer a new bio-based surfactant platform showing several benefits compared to commercially available sugar-based surfactants like alkyl polyglycosides or sorbitan esters. Six different grades of Glucamides have been scaled up from laboratory via pilot plant to full production scale.



Clariant offers these sugar-based surfactants especially developed for several application fields, for example Personal Care, Industrial and Home Care as well as Crop Solutions. The renewable products reveal very good cleaning performance, high mildness, excellent sensorial benefits and outstanding thickening properties.

[1] Sustainability Report 2015, Clariant
[2] Y.-P. Zhu, M. J. Rosen, P. K. Vinson, S. W. Morrall, *J. Surf. Deter.* **1999**, *2*, 357-362.
[3] J. J. Scheibel, D. S. Connor, R. E. Shumate, J. C. T. R. B. St. Laurent, EP0558515 (B1), Priority: **1990**.

Discovery of the cathepsin S inhibitor RG7625 for the treatment of autoimmune diseases

Wolfgang Haap

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wolfgang.haap@roche.com

The lysosomal cysteine protease cathepsin S plays an important role in antigen presentation by degrading the invariant chain fragment p10 to CLIP. This CLIP fragment is associated to the major histocompatibility complex MHCII. After exchange of CLIP by antigens the MHCII/antigen complex is transported to the surface on antigen presenting cells such as microglia, dendritic and B-cells. This complex may be recognised by e.g. T-cells which subsequently become activated. If this process is disturbed, occasional loading of MHCII by self antigens may occur followed by an autoimmune response. Therefore, inhibition of cathepsin S may be an effective treatment of autoimmune diseases.

This presentation will cover the medicinal chemistry optimization of a series of cathepsin S inhibitors culminating in the identification of RG7625 as a highly potent and highly selective cathepsin S inhibitor. Aspects of structure based design, enzyme kinetics and multi dimensional optimisation will be highlighted. The preclinical profiling of RG7625 and clinical Phase I data will be outlined as well.

Enantioselective synthesis of Insecticidal Isothiazolines

Myriem El Qacemi, Jérôme Cassayre, Peter Renold, Fabien Barreteau

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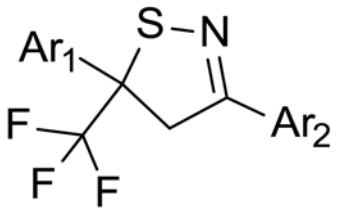
e-mail: myriem.el_qacemi@syngenta.com

2-Isothiazolines (also known as 4,5-dihydroisothiazoles) have been relatively unexplored as structural motif in life sciences, especially in agrochemistry. This might stems from the fact that, in sharp contrast, to their oxygenated counterparts, the 2-isoxazolines, very few general robust methods were available to synthetic chemists to prepare these heterocycles [1].

In recent years, we became interested to evaluate the potential of these moieties as replacement of 2-isoxazolines within one of our insecticidal projects. Our target heterocycles also featured a quaternary center, bearing a trifluoromethyl group, for which the stereoconfiguration is crucial for biological activity.



We herein describe the various strategies we investigated to access the desired 3,5-diaryl-5-(trifluoromethyl)-4H-isothiazoles, and then highlight the discovery of an efficient and unprecedented enantioselective synthesis of these heterocycles.

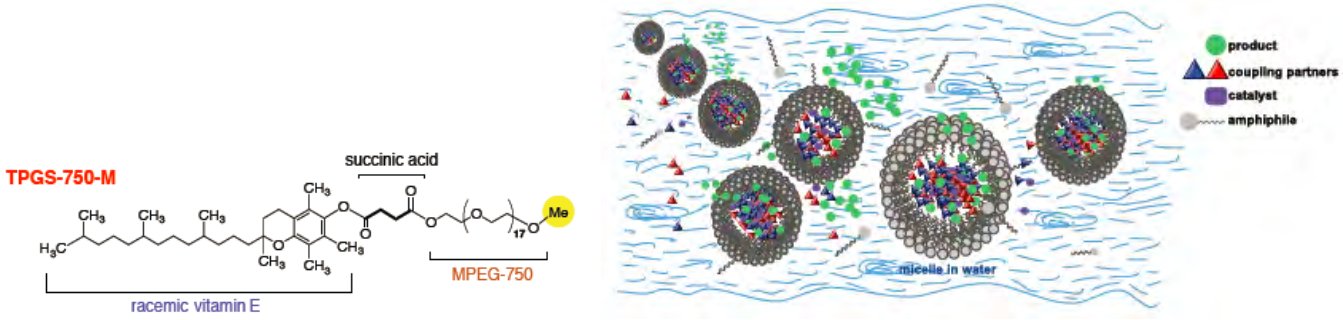
[1] Brown, D. W.; Sainsbury, M., Science of Synthesis, **2002**, *11*, 507-572.

Alternative solvents: from a compliance-driven activity to a trigger for innovation

Fabrice Gallou

Chemical & Analytical Development, Novartis Pharma AG, 4056 Basel, Switzerland.
E-mail: fabrice.gallou@novartis.com

During our evaluation of the potential of surfactant technology in collaboration with Professor Lipshutz,[1,2] we have identified a variety of straightforward and highly advantageous transformations and applied them successfully on-scale.[3] Implementation of the technology typically results into significant benefits across our entire portfolio, not just from an environmental standpoint but also from an economic and productivity perspective. To name a few: Reduction of organic solvent consumption, water use and cycle time, milder reaction conditions, improved yields and selectivities, which all contribute to improved process performance and lower manufacturing costs.[4]



Modern no-ionic surfactants for micellar catalysis in water.

These surfactant mediated reactions can be up-scaled in the already existing multi-purpose facilities of pharmaceutical or chemical organizations, using a catalytic amount of a combination of a non-ionic designer surfactant (e.g. TPGS-750-M) in water, and a well-chosen organic co-solvent instead of traditional and undesirable organic solvents.[5]

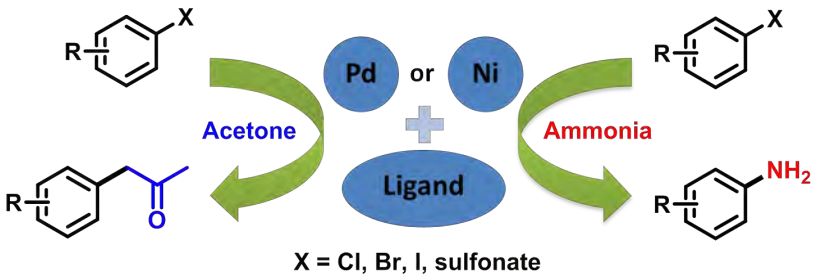
[1] See for example: *Science* **2015**, *349*, 1087; *Ang. Chem. Int. Ed.* ***2016****, 55, 8979; Ang. Chem. Int. Ed.* ***2016****, 55, 4914.*
[2] *J. Am. Chem. Soc*. **2013**, *135*, 17707; *Org. Lett*. **2015**, *17*, 4734; *Org. Lett*. **2015**, *17*, 3968; *Org. Proc. Res. Dev*. **2016**, *20*, 1104.
[3] *Green Chem.* ***2016****, 18, 14.*
[4] *ACS Sustain Chem. Eng*. **2016**, accepted.
[5] *Org. Proc. Res. Dev*. **2016**, *20*, 1388.

Catalysis @ Solvias - From Science to Business

Johannes Schranck, Jürgen Rotzler

Solvias AG, Römerpark 2, 4303 Kaiseraugst, Switzerland, johannes.schranck@solvias.com

The catalysis team at Solvias has been at the forefront of making the latest scientific findings available to the development of commercial catalytic processes.[1] Various transformations (i.e. asymmetric hydrogenation, C-C and C-X cross-couplings, asymmetric C-C bond formations) can be evaluated efficiently on the high throughput experimentation (HTE) platform. This platform is operated in conjunction with a large library of (chiral) ligands and thus represents a unique set-up for the investigation of homogeneously catalyzed reactions.



Following the concept of modularity, Solvias peruses the consistent expansion of its ligand portfolio. The resulting large variety of modular (chiral) ligands has, in turn, led to unprecedented findings in academia. For example, significant progress has recently been made in the monoarylation of ammonia and acetone.[2] More precisely, the application of ferrocenyl bisphosphine ligands has enabled significant progress in substrate scope, reaction conditions, as well as catalyst costs and availability. Examples of these ligands and transformations will be presented.

[1] H.-U. Blaser, B. Pugin, F. Spindler, *Top. Organomet. Chem.* **2012**, *42*, 65−102.
[2] J. Schranck, J. Rotzler, *Org. Process Res. Dev.* **2015**, *19*, 1936–1943.

What can academia learn from industry?

Dr. Christian Lothschütz

Siegfried AG, Zofingen
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Chemistry is an empirical science which is based on the exact planning, execution and description of experiments. In a recently published article Prof. Robert G. Bergman and Prof. Rick L. Danheiser discuss the problem of reproducibility of chemical experiments.[1] Amongst others, one of their conclusions is that in most cases non-reproducible results should not be traced back to planned scientific deception but to prejudiced authors or inaccurate notes. In process research and development, the detailed description and documentation of results is of central importance. For that reason, many individuals and companies working in this field try to capture this topic by the implementation of key performance indicators and other control mechanisms. In contrast to academia, industrial research is mostly driven by economic reasons. Ideally, the result of a process research and development program is a scalable and robust chemical process delivering products of constant quality. Based on this economic requirement, industrial researchers are facing strong needs for absolute transparency and compliance with standards (e.g. GMP standards), which are not present in academic research. In this short talk, the topic and the resulting problems as well as the proposed solutions by professors Bergman and Danheiser will be discussed.

Chemie ist eine empirische Wissenschaft, die auf der exakten Planung, Ausführung und Beschreibung von Experimenten beruht. In einem kürzlich erschienenen Artikel diskutieren die Professoren Robert G. Bergman und Rick L. Danheiser das Problem der Reproduzierbarkeit von chemischen Experimenten.[1] Unter anderem kommen Sie zu dem Schluss, dass in den meisten Fällen nicht nachvollziehbare Ergebnisse nicht auf bewusste Täuschung zurückzuführen sind, sondern vielmehr auf Befangenheit der Autoren oder fehlerhafte bzw. unvollständige Beschreibung und Interpretation der durchgeführten Experimente. In der Prozessforschung und -entwicklung ist die detaillierte Erfassung und Dokumentation aller Ergebnisse von zentraler Bedeutung. Daher wird vielfach versucht, diese Thematik durch Leistungskennzahlen und andere Mechanismen kontrollierbar zu machen. Im Gegensatz zu der akademischen Forschung dient die industrielle Forschung oftmals einem ökonomischen Zweck. Idealerweise steht am Ende einer Prozessentwicklung ein skalier- und technisch machbarer Prozess, welcher Produkte von gleichbleibender Qualität liefert. Aus der ökonomischen Anforderung entsteht folglich ein Zwang zur Transparenz und Einhaltung von geforderten Mindeststandards (beispielsweise GMP Standards), der in der akademischen Forschung nicht vorhanden ist. Dieser kurze Vortrag wird dieses Thema diskutieren und einige Probleme und vor allem die Lösungsvorschläge der Professoren Bergman und Danheiser vorstellen.

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Pilot Plant Production of a P2Y$_{12}$-Antagonist Containing (R)-3-Phosphonoalanine

Stefan, Abele

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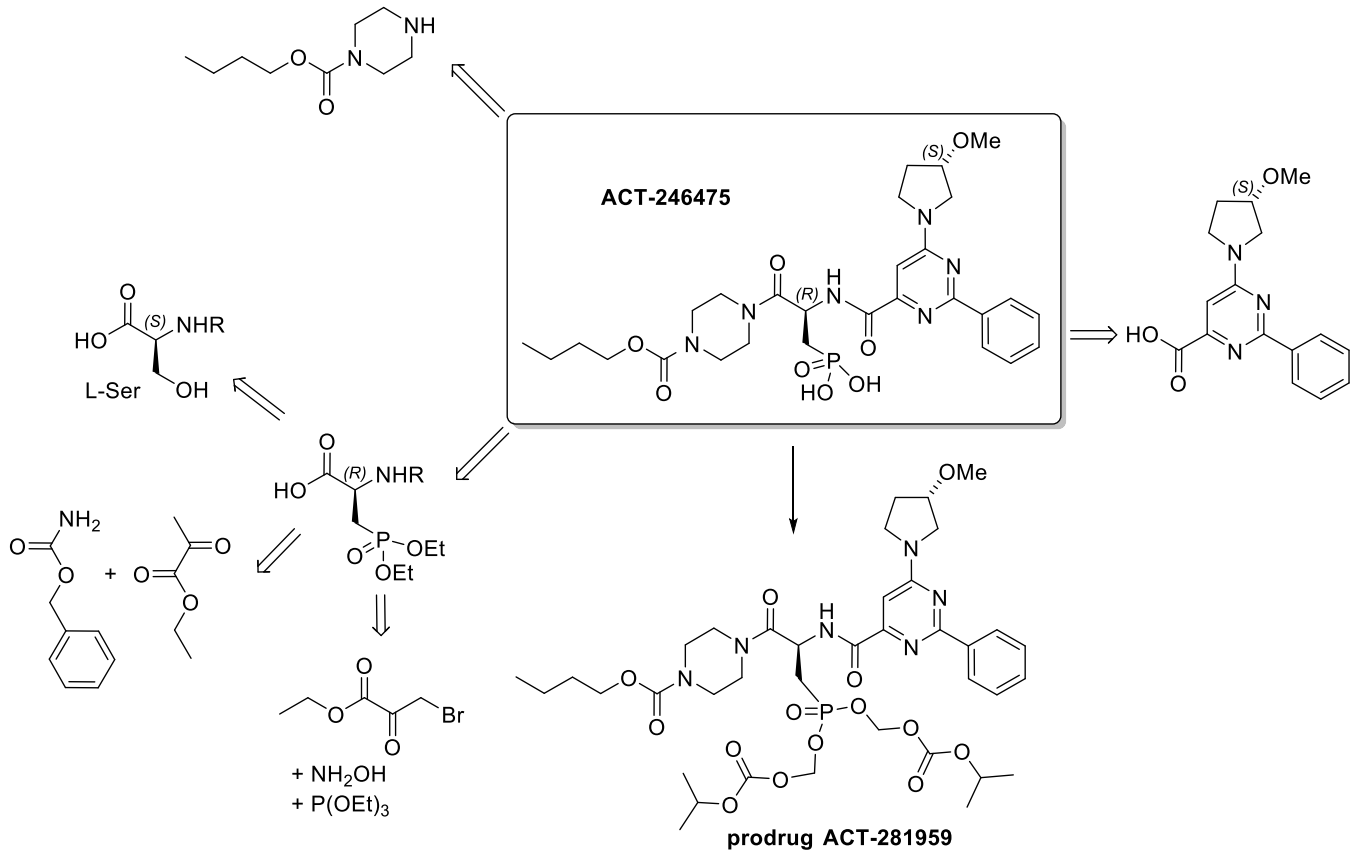
ACT-246475 is a P2Y$_{12}$ antagonist for inhibition of platelet aggregation that was selected for clinical development at Actelion Pharmaceuticals Ltd. It features several challenges for scale-up, like two chiral centres, the lack of solid intermediates, 18 chemical steps, and, specifically, the large scale production of enantiomerically pure non-natural amino acid (*R*)-3-phosphono alanine that was lacking a scalable access. The production of a pro-drug of **ACT-246475**, namely **ACT-281959** posed formidable challenges for the isolation and purification as it is a highly viscous oil (glassy). The evolution of the routes from Medicinal Chemistry to GMP manufacturing of **ACT-246475** is described, thereby highlighting the solutions to safely and reproducibly scale up the process. 2nd Generation processes to cut the Cost of Goods and to raise robustness and throughput are presented.



Process development aspects of alkylnitrites

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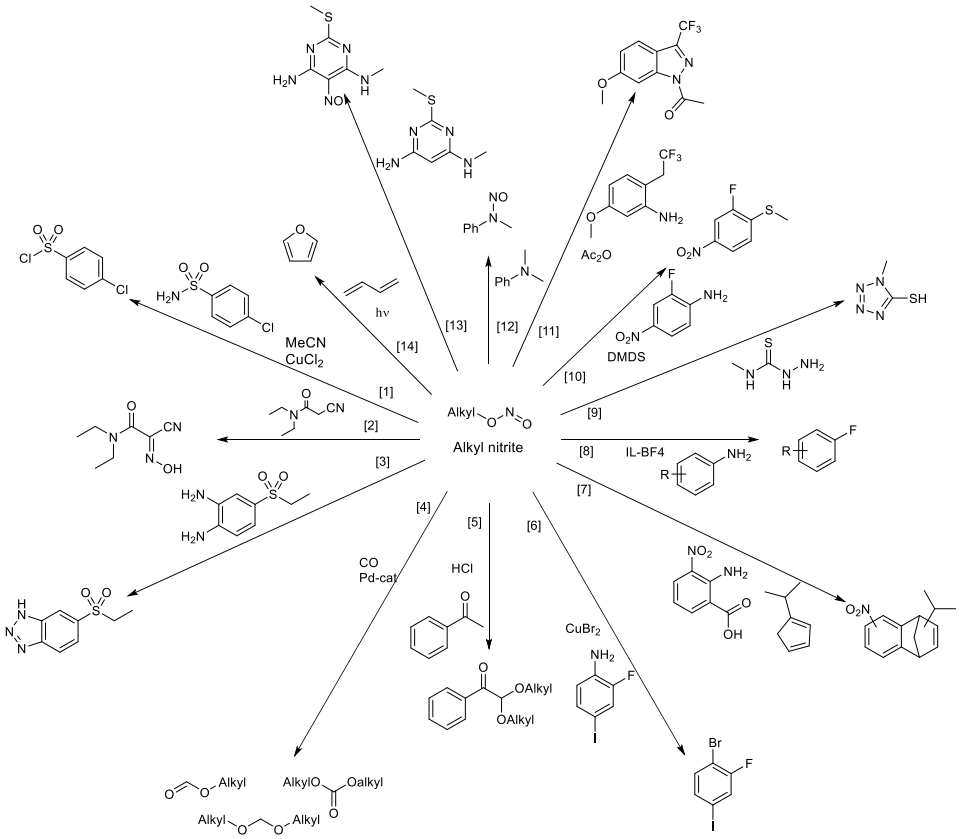
Alkylnitrites are versatile reagents usable for a fast amount of chemical transformations.



In order to provide valuable intermediates such as alkylnitrites for numerous applications, not only detailed physical properties need to be considered but also knowledge of principal applications is essential for the process development of these alkylnitrites.

In this talk, some process development aspects of alkylnitrites are discussed.

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Advanced Process Development into Future

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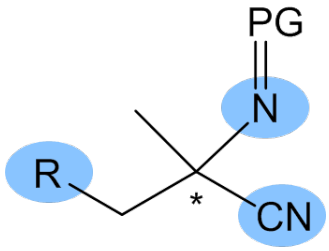
The lecture outlines an innovative process design approach enabling a new access to quarternary N-protected α-Methylaminonitrils.



R = OH, Ph, *i*-Pr

Such advanced key intermediates can be widely used and their manifold applications are based on three functional groups with different reactivities and the availability of both of their enantiomers in high yield and purity.

An originally racemic synthesis route leading to an API could be successfully transformed by using this novel chiral building block to an enantiomeric pure synthesis with significant economic advantage. The existing route with seven steps could hence be reduced to only three steps.

Key words: Enantiopure α-Methylaminonitrils, stereoselective synthesis; industrial process, Hazardous Reaction.

Poster Abstracts

Palladium-Catalyzed Enantioselective Intermolecular Carboetherification of Dihydrofurans

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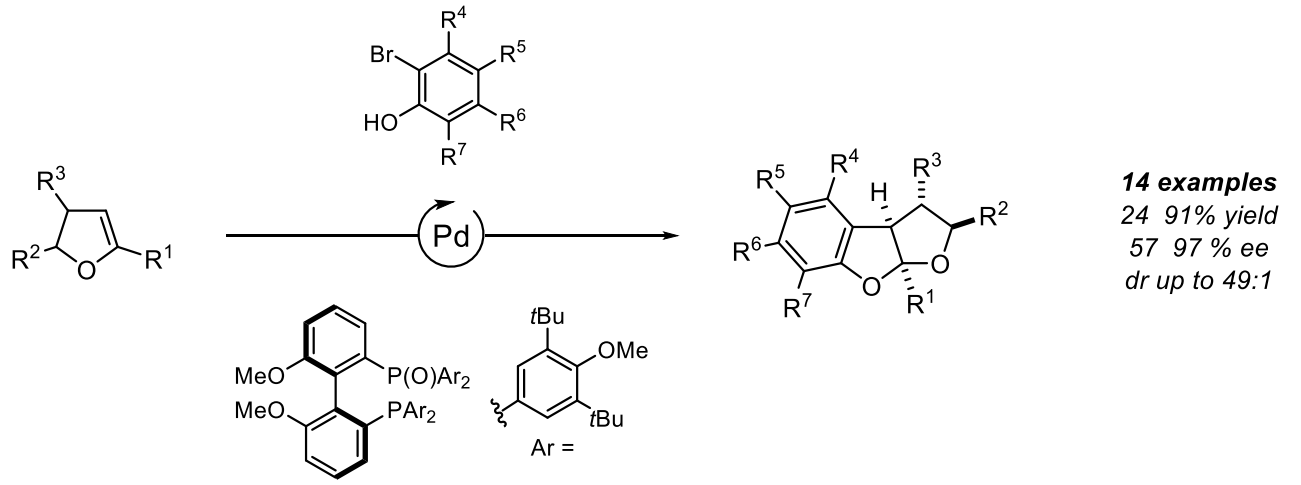
In recent years, efforts have been focused on the development of new methodologies for carbon-heteroatom bond formation,[1] owing to the ubiquity of aryl C-N and C-O bonds in agrochemicals, pharmaceuticals and natural products. Among these methodologies, the Pd-catalyzed carboetherification of alkenes has emerged as a powerful strategy. Despite remarkable advances in the field, most reported examples proceed via intramolecular reactions and their enantioselective variants are still scarce.[2,3]

Herein we describe a novel intermolecular carboetherification that gives direct access to fused tetrahydrofurobenzofurans; a scaffold that can be found in numerous biologically active compounds and which is tipically accesible via long and unpractical synthetic routes.[4] Under optimized conditions and using readily available starting materials, the final cross-coupling products are systematically obtained in high yield, enantio- and diastereoselectivity.[5] A key feature of our methodology is the *in situ* formation of a chiral bisphosphine mono-oxide (BPMO).



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Enantioselective Aldol Reactions with Masked Fluoroacetates

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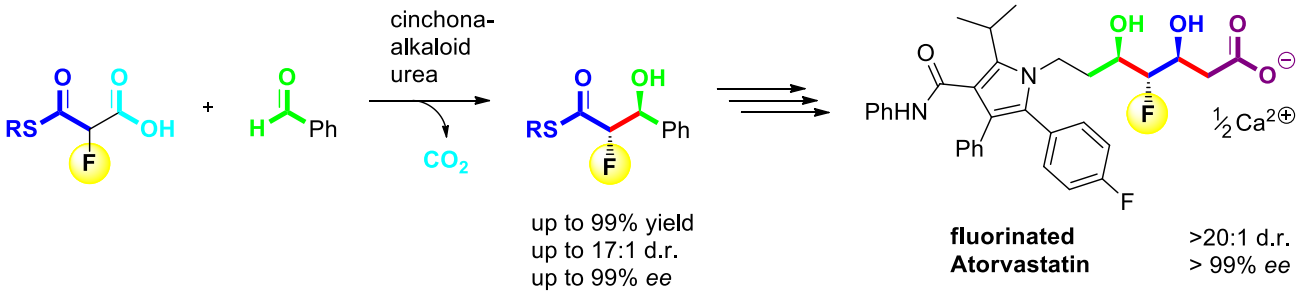
The incorporation of fluorine into organic molecules represents a versatile tool to influence its properties. The resulting increase in lipophilicity, activity and metabolic stability is particularly important for pharmacologically active substances.[1] However, fluorine containing natural products are hardly reported[2] and synthetic methodologies for its stereoselective introduction are limited.[3] One long-standing unsolved challenge is the enantioselective aldol reaction of fluoroacetate, which provides access to medicinally relevant polyketides and statins.

Herein, we present the development of fluoromalonic acid halfthioesters (F-MAHT) as biomimetic fluoroacetate surrogates as well as their application in highly stereoselective aldol reactions.[4,5] Under mild organocatalytic conditions, the α-fluorinated addition products were generated in good yields and diastereoselectivities and with up to 99% *ee*.



Scheme 1: Enantioselective Aldol reactions with masked fluoroacetates.

Furthermore, we demonstrated the synthetic value and versatility of the methodology by exploiting the unique reactivity of the thioester moiety of the products. Transformation into an aldehyde allowed us to perform consecutive aldol reactions to access fluorinated polyketide substructures, including a fluorinated analogue of top-selling cholesterol-lowering drug Atorvastatin (Lipitor®, Sortis®).

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Synthesis of a Stable Labelled Isotopomer of the CSF-1R Kinase Inhibitor BLZ945 and its Chemical Epimerization to the Pharmacologically Active cis-Isomer

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David Whitehead[a], Christian Guenat[b], Joel Krauser[a], Carsten Bauer[a,*]
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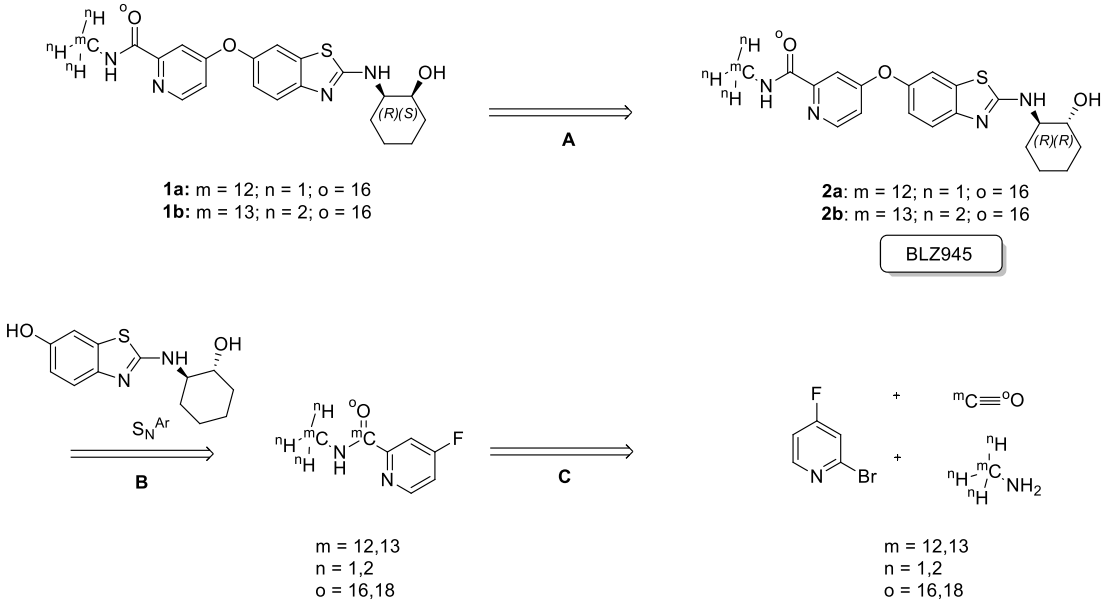
BLZ945 (**2a**), bearing a (1R,2R)-hydroxycyclohexylamino residue on C(2) of its benzothiazol core moiety, is a low molecular weight inhibitor of the colony stimulating factor 1 receptor (CSF-1R), which binds the cytokine M-CSF. Kinase inhibitors of this membrane protein found on macrophages have the potential to prevent metastasis in certain types of cancer. Recently, ten metabolites of BLZ945 were characterized after in-vitro incubation with human liver microsomes, hepatocyctes and recombinant P450[1]. Amongst these, the cis-isomer **1a** was identified as pharmacologically active. It was shown that the cis-metabolite **1a** accounted for 24% intrinsic clearance in human hepatocytes justifying the initiative to synthesize the stable labelled analytical standards **1a** and **2b**.

Here we present the development of a new synthesis of the isotopomer **2b.** Introduction of the label was achieved *via* amino-carbonylation of 2-bromo-4-fluoro-pyridine using a Xanthphos-based catalyst system with activation[2] (retro-step C). Nucleophilic aromatic substitution on this stable labelled building block used the enantiomerically pure hydroxyl-benzothiazol from our archive[3] (retro-step **B)**, followed by Mitsunobu epimerization to yield the cis-isomer **1b** (retro-step **A)**. Based on mechanistic studies with ^{18}O-labelling, we present indirect spectroscopic evidence for the presence of an activated intermediate in the Buchwald-Heck cycle.



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A New Class of Photoredox Catalysts: Robust Mo(0) Complexes as Earth-Abundant $[Ru(bpy)_3]^{2+}$ Analoga

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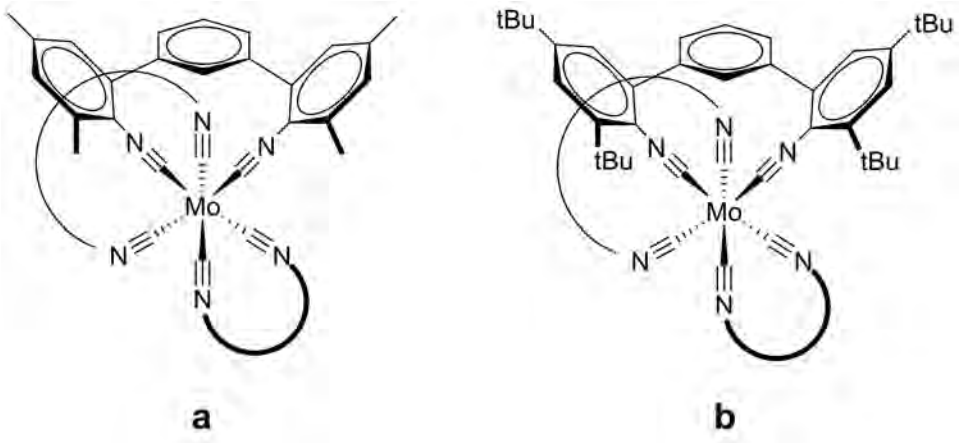
One of the best established classes of photosensitizers and photoredox catalysts are complexes derived from the ruthenium(II) tris(2,2'-bipyridine) complex. These compounds are chemically robust, exhibit MLCT absorptions in the visible spectral range, and their redox and photophysical properties are readily tunable by altering their ligands. [1]
Cr(0), Mo(0) and W(0) complexes with monodentate aromatic isonitrile ligands have been reported as isoelectronic analoga of these ruthenium complexes, but they are prone to photoinduced ligand dissociation. [2-3]



We recently reported on the first homoleptic Mo(0) complex with chelating isonitrile ligands (Fig. a).[4] Our complex is isoelectronic to $[Ru(bpy)_3]^{2+}$ and has similar optical spectroscopic properties, while offering much more reduction power than the ruthenium(II) parent compound. The chelating ligands make the complex rather robust and permit unusually challenging photoredox chemistry to take place. The application potential of the complex was put in evidence by employing it as a photocatalyst for an acyl-cyclopropane rearrangement reaction giving a 2,3-dihydrofuran compound in good yields.
The ligand was modified in order to optimize the excited states lifetimes as well as the chemical robustness of the complex (Fig. b). The new complex outperforms $[Ru(bpy)_3]^{2+}$ in terms of reducing power, excited-state lifetime, and luminescence quantum yield by far.
Our Mo(0) complexes are strongly reducing, chemically robust alternatives to $[Ru(bpy)_3]^{2+}$. They can be considered a new class of exceptionally strong photoreductants based on earth abundant metals.

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The role of substrate hydrogen bonding in the non-heme iron enzyme EgtB.

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Ergothioneine is an important cellular antioxidant that occurs in many bacteria, most fungi and also in human tissue.[1,2] The central step in ergothioneine biosynthesis is catalyzed by the non-heme iron enzyme EgtB. This enzyme mediates oxygen dependent sulfur – carbon bond formation between cysteine or γ-glutamyl cysteine and trimethyl histidine. In the active site of EgtB the two substrates are linked through a hydrogen bond between their amino acid moieties.[3] Due to geometric constraints this interaction must break in the course of the reaction. To elucidate the precise sequence of elementary steps during EgtB catalysis we examined the contributions of this hydrogen bond in substrate binding and transition state stabilization using substrate analogs and kinetic analysis.

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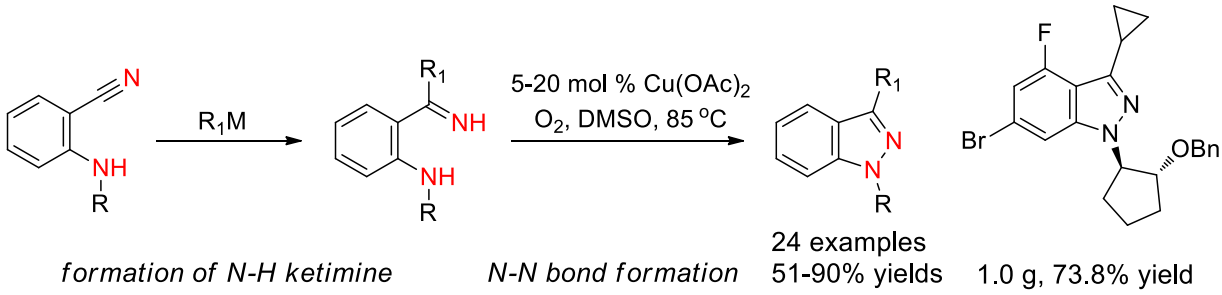
A Synthesis of 1*H*-Indazoles *via* a $Cu(OAc)_2$-catalyzed N-N Bond Formation

Cheng-yi Chen,[†] Guangrong Tang,[‡] Fengxian He,[‡] Zhaobin Wang,[‡] Hailin Jing[‡] and Roger Faessler[†]

[†]Janssen R&D, Pharmaceutical Development and Manufacturing Sciences, Small Molecule API Switzerland, Cilag AG, Hochstrasse 201, 8205 Schaffhausen, Switzerland
[‡]Porton (Shanghai) R&D Center, 1299 Ziyue Road, Zizhu Science Park, Minhang District, Shanghai 200241, China

A facile synthesis of 1*H*-indazoles featuring a $Cu(OAc)_2$-catalyzed N-N bond formation using oxygen as the terminal oxidant is described. The reaction of readily available 2-aminobenzonitriles with various organometallic reagents led to *ortho*-aminoaryl N-H ketimine species. The subsequent $Cu(OAc)_2$-catalyzed N-N bond formation in DMSO under oxygen afforded a wide variety of 1*H*-indazoles in good to excellent yields.



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Fully Substituted α-Aminonitriles as Versatile Intermediates Toward the Synthesis of Alkaloids

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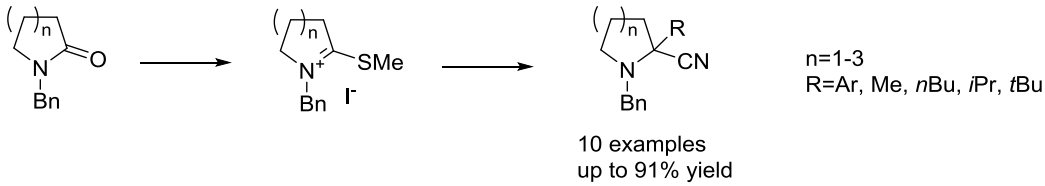
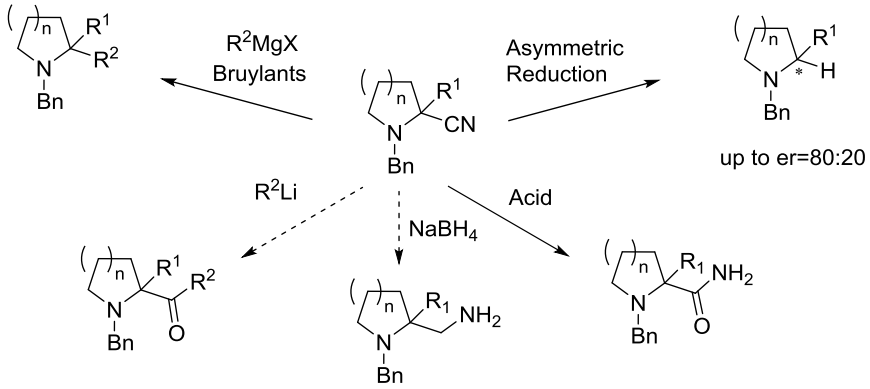
philippe.renaud@dcb.unibe.ch

An efficient and robust route toward fully substitued cyclic α-aminonitriles *via* thioiminium ions obtained from cyclic lactams was recently developed in our group. Quaternary α-aminonitriles were obtained in good yields after sequential alkylation-cyanation process.[1]



Nitrile groups are interesting moieties since they can be converted in one step into a variety of other functional groups, including primary amines, ketones, carboxylic acids (or esters), and amides. They are also stable precursors of iminium ions and enamines. Our work focused on the use of those later versatile intermediates and especially their asymmetric reduction.[2] The results are presented herein.



This strategy was successfully applied in the formal total synthesis of (±)-Cephalotaxine *via* the preparation of Tietze' s intermediate.[3]

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Swiss Stereoselective Organocatalyzed Synthesis of α-Fluorinated β-Amino Thioesters and their Application in Peptide Synthesis

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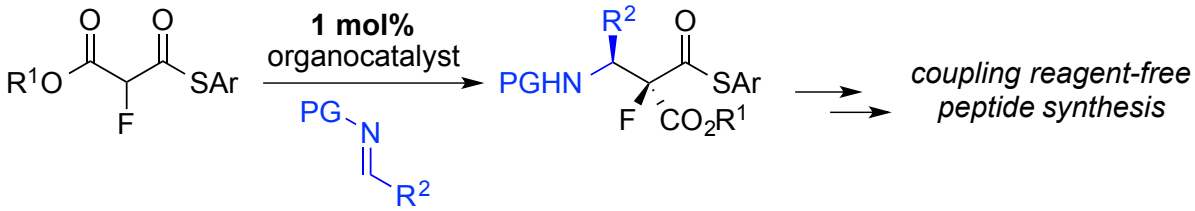
ETH Zürich, Laboratory for Organic Chemistry,
D-CHAB, Vladimir-Prelog-Weg 3, 8093 Zürich, Switzerland

Fluorination and the incorporation of *β*-amino acids into peptides represent powerful strategies to enhance their proteolytic stability and to control their conformation.[1] These features are combined in *α*-fluoro-*β*-amino acids, which influence the conformation of *β*-peptides.[2] However, the stereoselective synthesis of *α*-fluoro-*β*-amino acids is not straightforward.[3] Malonic acid half thioesters (MAHTs) and monothiomalonates (MTMs) have been recognized as valuable thioester enolate equivalents for organocatalyzed addition reactions.[4,5] Recently, our group developed a stereoselective method to access fluorinated aldol products using fluorinated malonic acid half thioesters (F-MAHTs) as building blocks.[6]

Herein we present highly stereoselective organocatalyzed Mannich reactions between fluorinated monothiomalonates (F-MTMs) and *N*-Cbz and *N*-Boc protected imines.[7] The methodology requires only 1 mol% of organocatalyst and provides access to the corresponding *α*-fluoro *β*-amino thioesters, which can be used for coupling reagent-free peptide synthesis in solution and on solid phase.



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Development and applications of C(sp^3)–H Alkenylation

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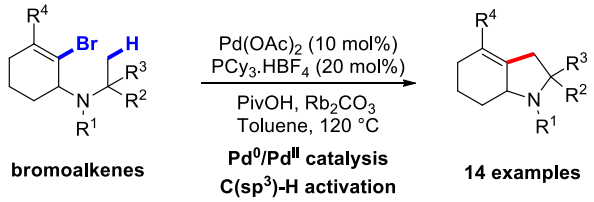
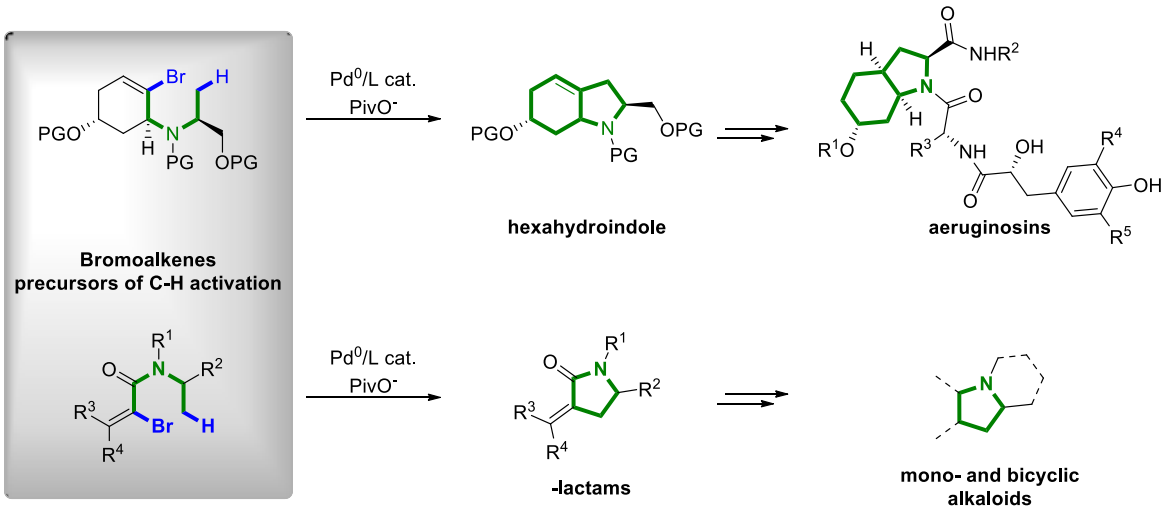
In the last decade, the transition metal-catalyzed intramolecular activation of unactivated C-H bonds has emerged as powerful method to transform otherwise inert entities.[1] Within this field, we recently developed a straightforward access to hexahydroindoles by intramolecular C(sp^3)-H alkenylation starting from bromoalkenes.[2]



In this communication, we will report access to alkaloids by use of this intramolecular C(sp^3)-H alkenylation. Firstly, the combination of this methodology with a directed C(sp^3)-H arylation allowed to achieve a divergent synthesis of aeruginosins.[3] In a second part, the development of a modular C(sp^3)-H alkenylation leading to β-lactams,[4] which are prevalent scaffolds found in numerous bioactive natural molecules, will be described.



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Bicyclopyrone: Chemistry Transforming Weed Control

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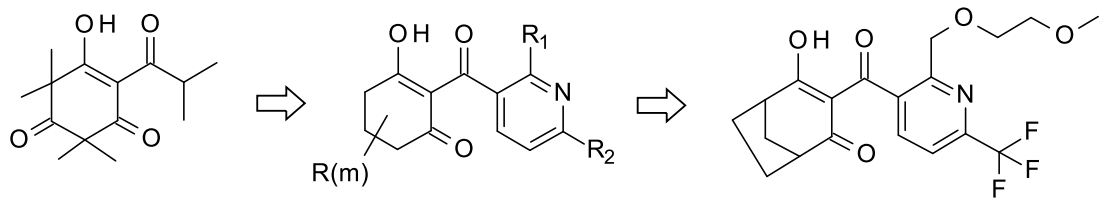
Bicyclopyrone (scheme) is a novel triketone herbicide is as a highly potent, but beautifully selective, corn herbicide. It was launched in 2015 in a 4-way mixture with the trade name Acuron™, but products with bicyclopyrone as a single component (Acuron-UNO™) have also reached the market place. This poster highlights the discovery of bicyclopyrone, which began from the naturally occurring HPPD inhibitor *leptospermone*, further development to the nicotinoyl cyclohexane diones, and ultimately transformation to the market product. Synthesis of the nicotinoyl cyclohexane diones is discussed as well as the biological activity of the optimised member of this class, bicyclopyrone.

Scheme



Leptospermone | Nicotinoyl cyclohexane diones | Bicyclopyrone

Kiegiel-Type Reactions for the Efficient Synthesis of Dioxinone β-Keto-esters and Derived Terpenoid Resorcylates: Total Synthesis of (±)-Daurichromenic and (±)-Cannabiorcichromenic Acids

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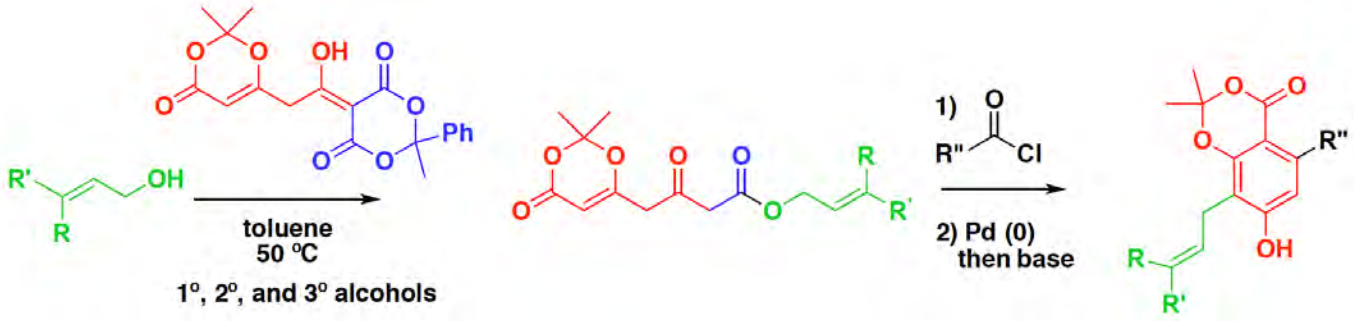
The 6-alkyl-2,4-dihydroxybenzoic acid or β-resorcylic acid moiety is a structural element present in many biologically active natural products. Over the past decade our group has developed a biomimetic strategy to synthesize resorcylate natural products that utilizes a palladium-catalyzed decarboxylative allylic migration and aromatization sequence of dioxinone β-keto-esters.[1] We have recently developed an efficient Kiegiel-type reaction to synthesize these key intermediates with an improved yield and scalability.[2] The new methodology will presented, along with its application to the total synthesis of the natural products (±)-daurichromenic and (±)-cannabiorcichromenic acids.



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Stereoselective Organocatalytic Synthesis of *β*-Amino Thioesters and their Synthetic Application

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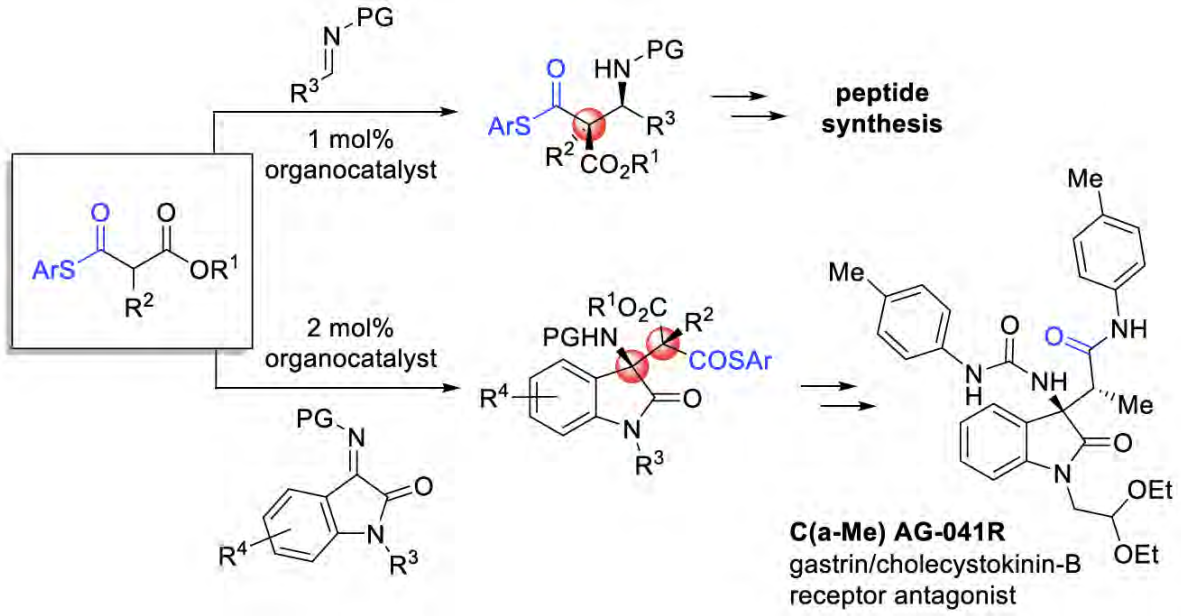
Thioesters are versatile building blocks for subsequent transformations into other functional groups such as ketones, aldehydes or amides. Nature utilizes malonic acid half thioesters (MAHTs) as thioester enolate equivalents in the biosynthesis of fatty acids and polyketides. MAHTs have also been used in organic synthesis but suffer from uncontrolled decarboxylation. Our group introduced mono thiomalonates (MTMs) as protected variants of MAHTs and versatile surrogates of thioester enolates.1 Herein we present highly stereoselective synthesis of *β*-amino thioesters that proceed under mild organocatalytic conditions through Mannich-type addition reactions of MTMs to *N*-Cbz and *N*-Boc protected imines. The method provides valuable building blocks for coupling-reagent-free peptide synthesis.2,3 In addition, this methodology also allowed for the synthesis of 3-substituted 3-amino-2-oxindoles containing two adjacent tetrasubstituted stereocenters. We show the synthetic value of the differentially functionalized oxindoles for the synthesis of derivatives of the bioactive *β*-amino acid AG-041R.4



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Stereoselective Arene-Forming Aldol Condensation: Synthesis of Axially Chiral Aromatic Amides

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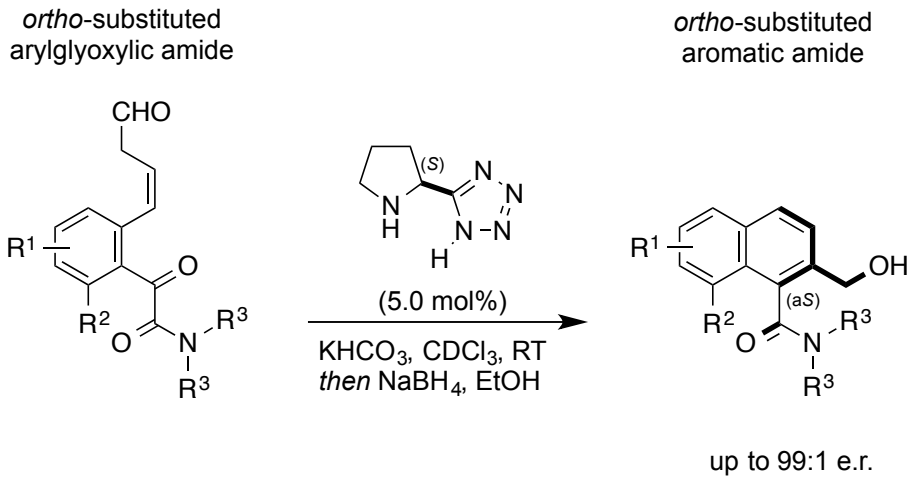
Aromatic amides are among the most valuable structural motifs for the synthesis of bioactive compounds. In the case of a substitution pattern leading to a restricted Ar–CO rotation, complex conformational features and atropisomerism can frequently be observed. However, the selective preparation of these aromatic amide atropisomers still remains synthetically challenging. Today, only two strategies for the stereoselective catalytic preparation of Ar–CO rotationally restricted aromatic amides have been reported, while the importance of axially chiral aromatic amides as auxiliaries, ligands and organocatalysts is established.

The poster will outline the stereoselective synthesis of configurationally stable aromatic amides by an atroposelective arene-forming aldol condensation. Ortho-substituted arylglyoxylic amides precursors are converted into the corresponding axially chiral aromatic amides by a chiral secondary amine catalyzed process. Nearly complete transfer of the stereochemical information of the catalyst into axially chiral aromatic amides was achieved within minutes at ambient temperature to obtain highly enantioenriched ortho-substituted aromatic amides.



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Exploring Site Selectivity of Iridium Hydride Insertion into Allylic Alcohols: Serendipitous Discovery and Comparative Study of Two Catalysts for the Vinylogous Peterson Elimination

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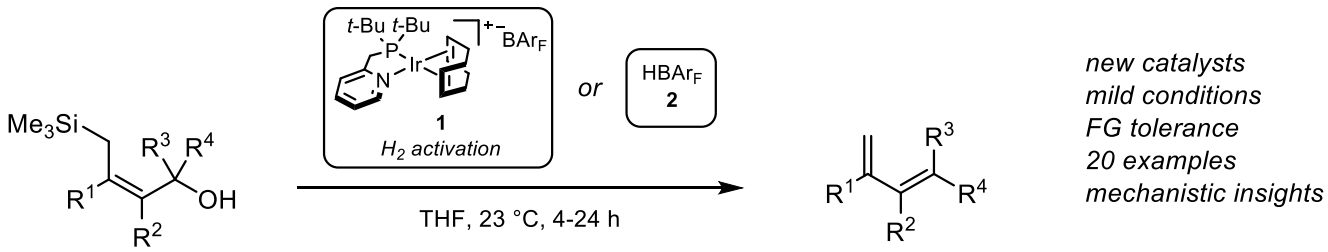
The 1,2-migratory insertion of an olefin into a transition metal hydride is a fundamental elementary step in organometallic chemistry that constitutes the basis of a plethora of catalytic processes.[1] In recent years, our group has pursued the development of iridium complexes of general formula [(P,N)Ir(cod)]BAr_F for the enantio- and diastereoselective isomerization of primary allylic alcohols to aldehydes.[2] Productive isomerization proceeds via an intermolecular hydride-type mechanism involving insertion of the in situ generated [Ir−H] intermediate across the C=C bond of the allylic alcohol, followed by β-hydride elimination and tautomerization to deliver the carbonyl compound.[2a]

Herein we describe how attempts to control site-selectivity of [Ir−H] insertion by introduction of a silyl substituent in the vicinity of the C=C bond of the allylic alcohol led to the serendipitous discovery of two novel and complementary catalytic systems for the vinylogous Peterson elimination: (i) an [Ir−H] catalyst generated upon activation of **1** by molecular hydrogen and (ii) an unusually mild Brønsted acid catalyst ($HBAr_F$ (**2**)).[3] Preliminary studies revealed two distinct mechanistic pathways are operating. Optimization of this rather underdeveloped reaction was pursued to afford a variety of 1,3-dienes in excellent yields. Remarkably, the mild reaction conditions under which **1** and **2** operate are compatible with sensitive functional groups that would not be tolerated by more conventional acidic or basic reagents. [4]



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Direct Transformation of Esters into Heterocyclic Compounds: Synthesis of Fluorescent Dyes

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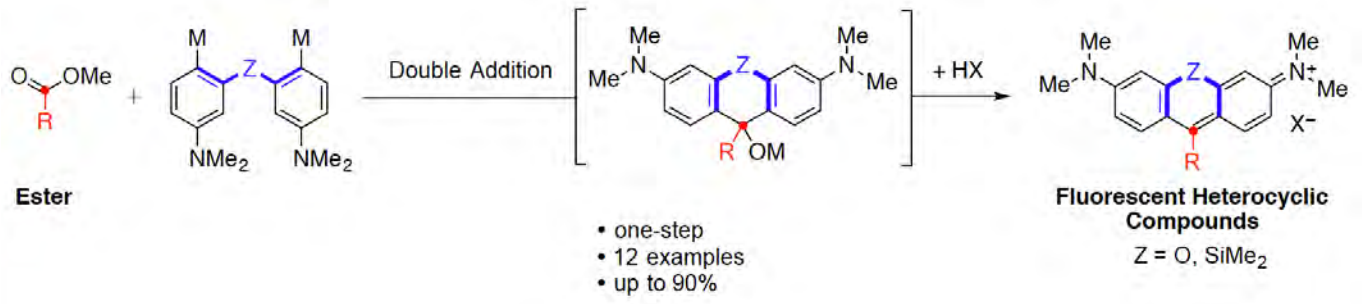
Heterocyclic compounds are of considerable importance in material science as well as medicinal chemistry. Therefore, efficient and environmentally benign methods for the synthesis of heterocyclic compounds are required. Xanthylium based small–molecule fluorophores are a class of heterocycles which are known for over a century and have become essential for the visualization of biomolecules and biochemical events, e.g. to support the understanding of diseases. However, the synthesis of such small–molecule fluorophores bear unsolved syntheses issues and the currently high interest in small–molecule fluorophores demand a highly flexible and direct synthesis with the use of stable reagents.

Motivated by our previous results in the synthesis of arenes, we set out to investigate a one-step synthesis of heterocycles from carboxylic acid esters in combination of 1,5-bifunctional organomagnesium reagents. With a heteroatom incorporated in the 3-position of the 1,5-bifunctional reagent (Z = O or $SiMe_2$), we would obtain a heterocyclohexadienolate intermediate which forms a fluorescent salt upon acidic work-up, when substituted with an amino group.

This highly modular approach led to the formation of aryl, alkyl and alkenyl xanthylium dyes (X = O) and SiR-dyes (X = $SiMe_2$) dyes in up to 90% yield. This approach is expected to become the preferred method for the formation of fluorescent dyes with tailored physicochemical properties.



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Phosphane Oxidation Catalyzed by Zerovalent Cobalt Complexes using Nitrous Oxide as Oxidant

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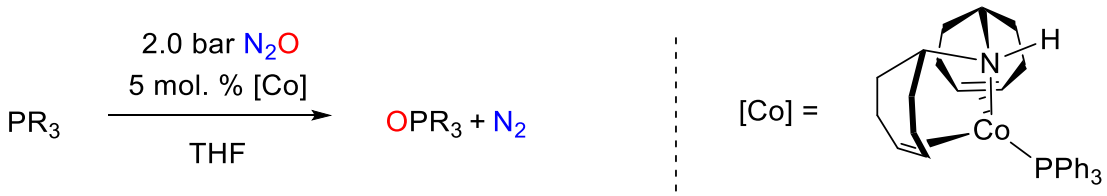
Nitrous oxide (N_2O) is industrially obtained as a by-product which has been recently identified as one of the largest global ozone depleting agents[1] and a greenhouse gas 300 times more powerful than CO_2.[2] Its transformation to less harmful chemicals is of particular interest but very challenging,[4] since even if thermodynamically unstable, nitrous oxide is kinetically inert.[3] Phosphine oxides are an important class of compounds with several applications: ligands in metal-catalyzed cross-coupling reactions (secondary phosphine oxides, $O{=}PHR_2$),[5] contact doping for silicon wafers and nanostructures, photoinitiators.[6] Traditional routes to their preparation (*e.g.* peroxides) are useful but present problems such as selectivity, functional group tolerance, complicated work-up and generation of chemical waste, and these route are not suitable for highly reactive or sensitive phosphines. The present work illustrates the use of zerovalent amino-olefin cobalt complexes in the selective oxidation of highly reactive phosphines using nitrous oxide as oxidant under mild reaction conditions.

Figure 1



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Stereoselective synthesis of trifluoromethyl containing cyclopropanes

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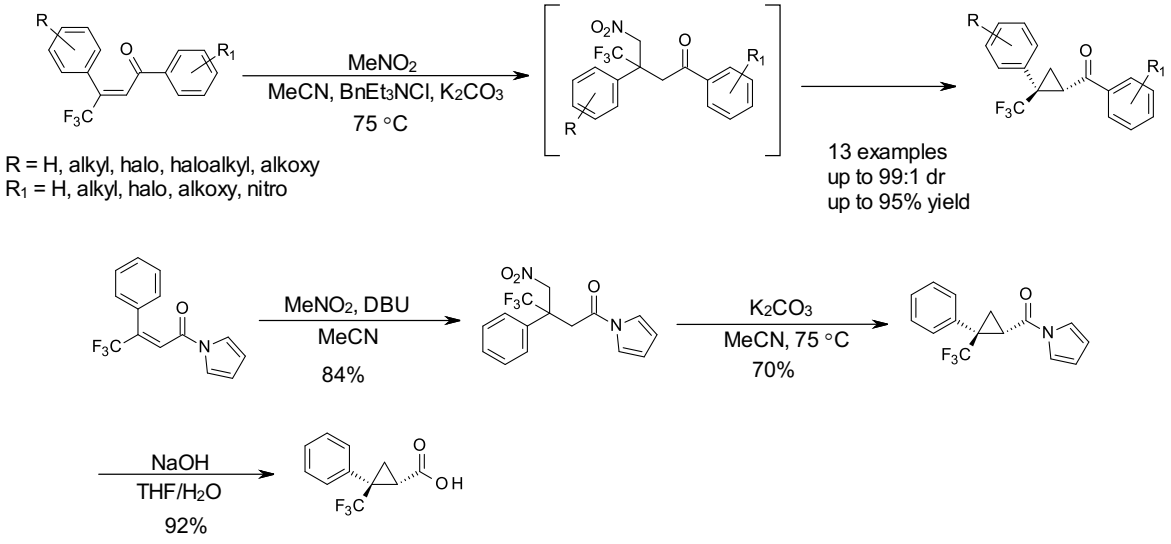
During the last decade there has been an increased attention in both academia and industry towards development of methods for incorporation of fluorine in organic molecules. The increased interest in fluorine chemistry arises from the fact that chemical and biological properties of small molecules are significantly altered by introduction of fluorine atoms and a significant percentage of drugs and agrochemicals contain fluorine atoms.[1]

Here we report a stereoselective cyclopropanation of β-trifluoromethyl chalcones using nitromethane as a source of methylene fragment. This methodology was also used for synthesis of corresponding carboxylic acid derivatives which are then amenable for further functionalization. Mechanism and origins of stereochemistry will also be discussed.



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Organolithium Chemistry in Flow: Continuous Synthesis of Boronic Acids within 1 second

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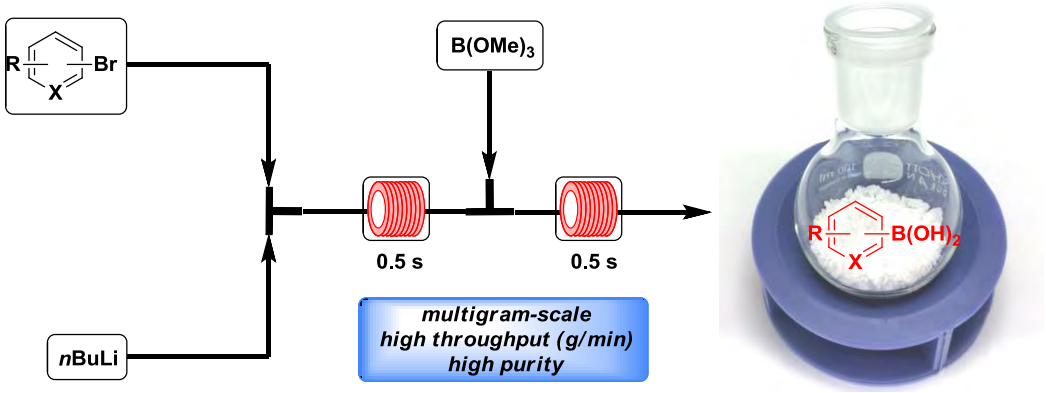
Continuous manufacturing (CM) or Continuous Flow Chemistry as a technical innovation aims to complement traditional batch operations by opening access to chemistries not easily accomplished in standard batch equipment, such as the handling of highly reactive or unstable intermediates.[1] As such, organolithium compounds are important intermediates in the pharmaceutical industry due to their high reactivity and broad applicability in organic synthesis.



Herein, we present the benefits and limitations of a simple continuous flow setup for handling and performing of organolithium chemistry on the multigram scale. The developed metalation platform embodies a valuable complement to existing methodologies, as it combines the benefits of *Flash Chemistry* (chemical synthesis on a time scale of <1 s) with remarkable throughput (g/min) while mitigating the risk of blockages.[2] The broad scope and high functional group tolerance was demonstrated by the synthesis of various boronic acids on multigram-scale (throughput ~ 300 mmol/h) in very high purity (>95% at 210 nm, after an extractive workup).

In addition a scale-up concept was developed, allowing for the rapid scale-up to even higher throughputs (~ 1800 mmol/h).[3]

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Controlling the Shape of bisFerrocene Macrocycles by the Bulkiness of the Substituents

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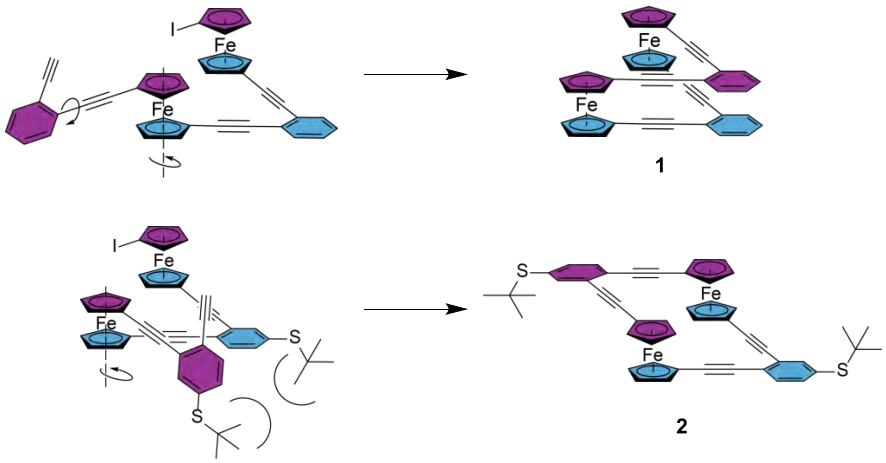
[b)] Karlsruhe Institute of Technology (KIT), Institute of Nanotechnology (INT), P.O.Box 3640, D-76021 Karlsruhe, Germany;
[c)] Lehn Institute of Functional Materials (LIFM), Sun Yat-Sen University, Guangzhou, China.

Herein we present the synthesis of two complementary bisferrocene macrocycles, build up via Sonogashira cross coupling and intramolecular ring closing reaction. While di-1,2-diethynylbenzene 1,1′-disubstituted ferrocene complex **1** shows a stacking behavior, the shape can be controlled by decorating the diethynylbenzene rings with bulky *tert*-butylsulfanyl groups, forming a stretched oriented bisferrocene complex **2**. The stretched rhomboidal structure further shows a dynamic behavior regarding the rotation along the ethynyl-Cp axis. The structural variation is studied by dynamic NMR spectroscopy and the electrochemical nature of the two complementary bisferrocene complexes is investigated via cyclic voltammetry.



Asymmetric Morita-Baylis-Hillman Reaction: Catalyst Design and Mechanistic Insights

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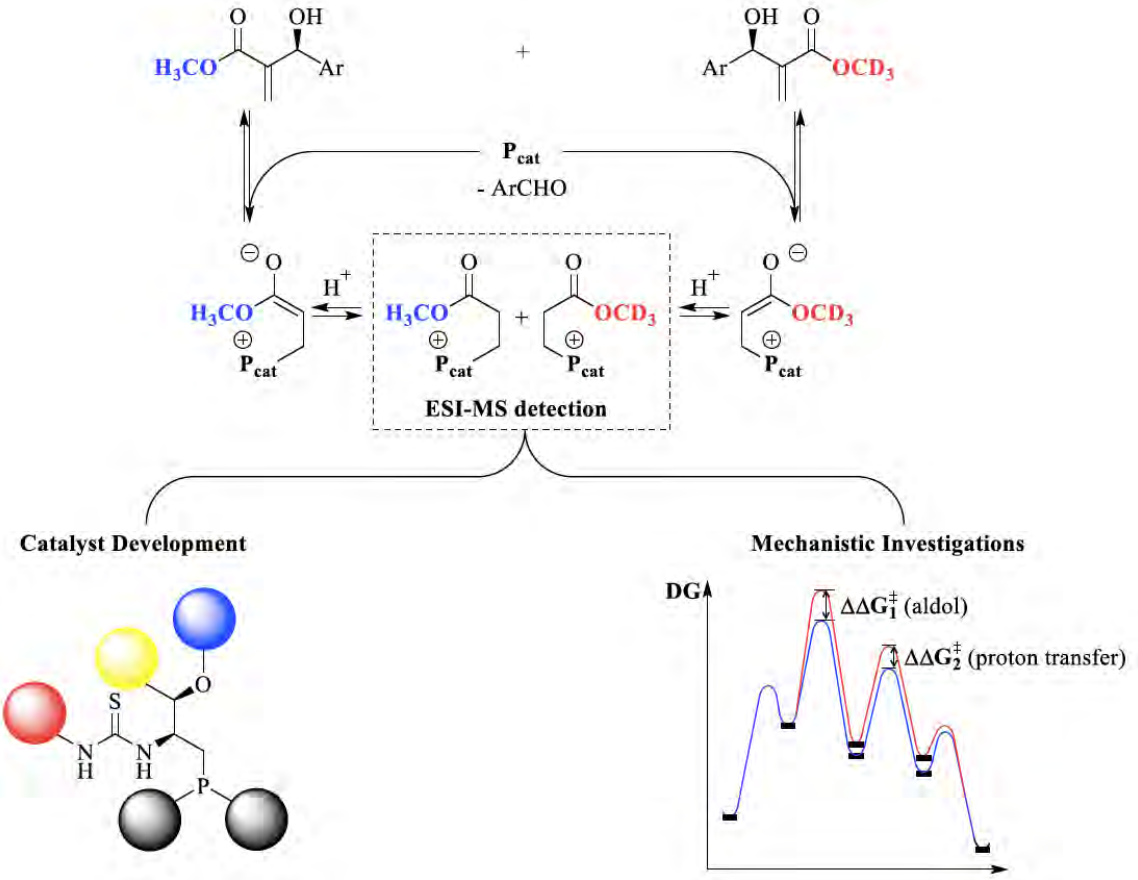
The Morita-Baylis-Hillman (MBH) reaction is a powerful method for the formation of a C-C bond between the α position of a Michael acceptor and an electrophile. The resulting products are highly functionalized building blocks, which can be easily modified in various ways. In the last decade substantial progress has been made in the development of enantioselective MBH reactions. However, although many chiral catalysts have been reported that give access to enantioenriched MBH products, their scope is generally limited. Especially for MBH reactions of simple acrylic esters with aldehydes, more efficient catalysts with a broader application range are needed. Herein we report a combinatorial approach to the development of chiral phosphine catalysts based on a mass spectrometric screening method devised in our laboratory, which has led to improved bifunctional chiral phosphine catalysts for MBH reactions of methyl acrylate with aldehydes. In addition, the data from mass spectrometric screening also allowed us to gain mechanistic insights and to identify the enantioselectivity-determining step in the catalytic cycle.[4]



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Synthesis and catalytic activity of triazolylidene iron(ii) piano stool complexes

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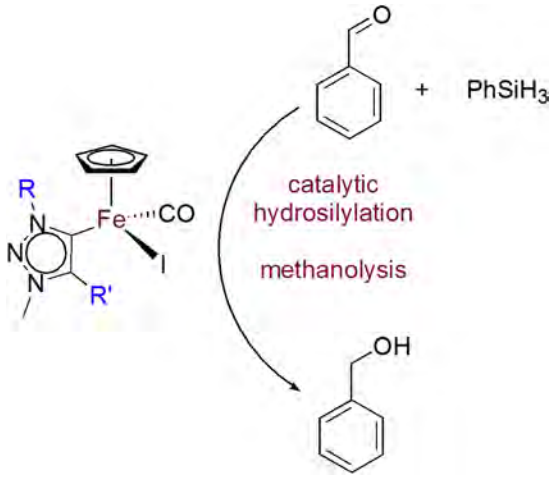
In recent years, mesoionic 1,2,3-triazolylidenes have emerged as a highly versatile subclass of N-heterocyclic carbene (NHC) ligands.[1] This NHC scaffold can be effectively tailored to specific functions as a consequence of the flexibility of the [3 + 2] cycloaddition of alkynes with azides. This feature, coupled with the ligands' strong σ-donor abilities have led to their diverse application in catalytic transformations.[2]

Despite the substantial economic advantages of iron based NHC catalysts vs the rare and heavy transition metals, examples are relatively scarce.[3] Herein we present a new class of triazolylidene iron(II) piano stool complexes and discuss their application in catalytic hydrosilylation reactions.



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Modifying spacers and anchoring groups for heteroleptic Cu(I) - 6,6'-dimethyl-2,2'-bipyridine based DSSCs

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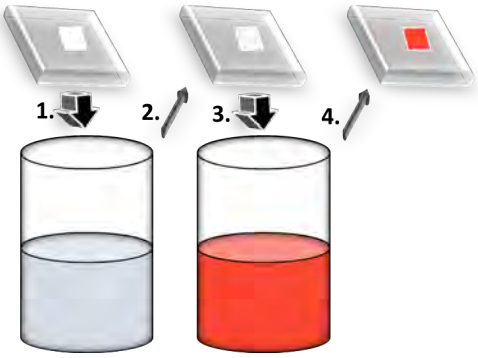
University of Basel

Heteroleptic $[Cu(6,6'\text{-dimethyl-2,2'-bipyridine})_A(6,6'\text{-dimethyl-2,2'-bipyridine})_C]^+$ (A: anchoring ligand, C: capping ligand) complexes in which the bpy units are functionalized in the 4- and 4'-positions are known to be good light harvesting materials in dye-sensitized solar cells (DSSCs). When the formation of isolated heteroleptic $[Cu(bpy)_A(bpy)_C]^+$ complexes is attempted, equilibration occurs giving mixtures of homo- and heteroleptic complexes; separation is very difficult. Therefore our group has developed a stepwise build-up of DSSCs (Figure 1a): a 'surface-as-ligand, surface-as-complex' approach.[1] For the first step a 6,6'-dimethyl-2,2'-bipyridine ligand, which is modified in the 4 and 4'-positions by a spacer bearing an anchoring group (e.g. 4-phenylphosphonic acid, Figure 1b) is bound to a TiO_2 surface. Afterwards Cu(I) and a capping ligand are introduced by a ligand exchange reaction between the anchored bpy_A and a bpy_C of the homoleptic $[Cu(bpy_C)_2]^+$ complex. In previous work done by our group, much focus was put on the modification of the capping ligand to enhance photo to current efficiencies. The standard anchoring ligand with the best performance, which is currently used in our group is shown below. Changing the anchoring group from phosphonic acid to alternative groups[2], as well as modifying the phenyl spacer to a thiophene spacer has been investigated[1] with a goal of enhancing solar cell performance for $[Cu(bpy)_2]^+$ complexes. Targets are to gain better affinity of the anchoring group to TiO_2, better electron transport through the spacer, less electron recombination between dye and electrolyte and an overall longer electron lifetime within the complex.

a)



b)

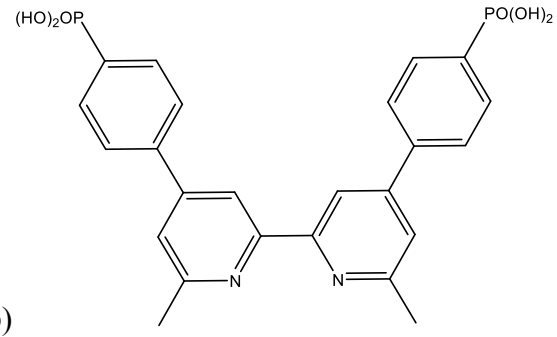


Figure 1: **a)** Preparation of heteroleptic $[Cu(bpy)_A(bpy)_C]^+$ complexes on TiO_2: 1. One day treatment of the TiO_2 coated glass plate in a solution of the anchoring ligand (1 mM in DMSO), 2. Cleaning, 3. Three days treatment of the modified TiO_2 surface with a homoleptic $[Cu(bpy_C)_2]^+$ complex, 4. Clean and fabrication of the DSSC. **b)** Current standard anchoring ligand bearing two 4-phenylphosphonic acid groups in the 4- and 4'-positions of 6,6'-dimethyl-2,2'-bipyridine.

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Synthesis of amino-cyclobutanes *via* [2+2] cycloadditions involving keteniminium intermediates

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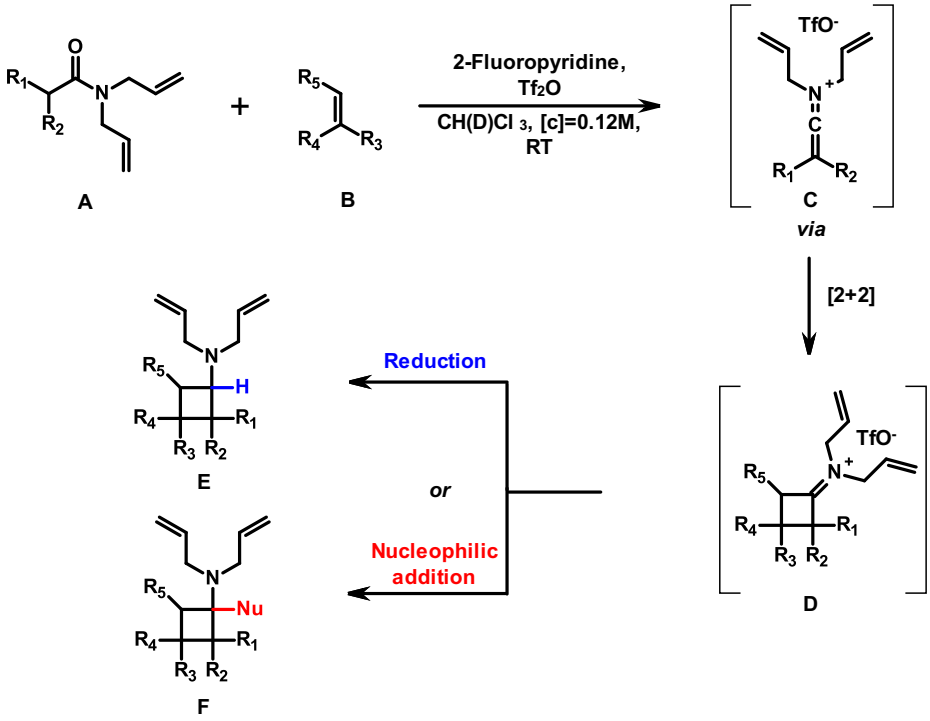
An efficient method has been developed for the synthesis of aminocyclobutanes *via* a [2+2] cycloaddition between a keteniminium salt and an alkene, followed either by a stereoselective reduction or a nucleophilic addition. The use of easily removable *N*-allyl moieties as protecting groups increases the potential of this method to access, in a few steps, highly functionalized cyclobutaneamines-containing building blocks. Moreover, competition reactions as well as DFT calculations verify the compatibility of *N*-allyl in [2+2] cycloaddition reactions.



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Chiral Ruthenium-cyclopentadienyl Complexes as Versatile Catalysts for Enantioselective Transformations

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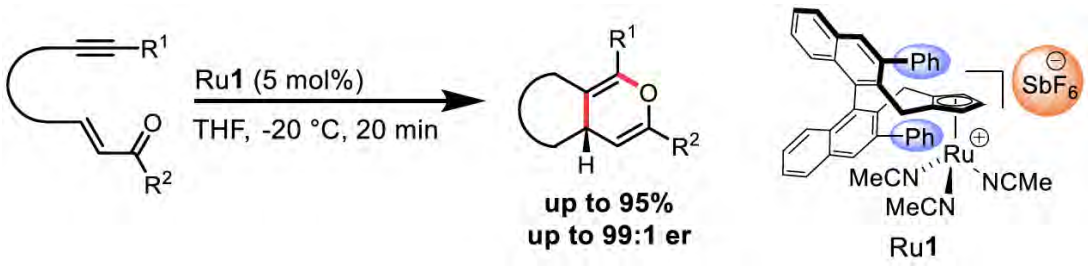
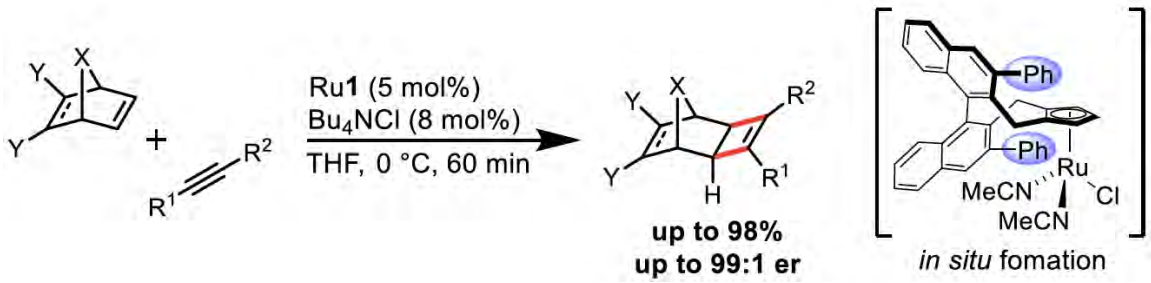
The cyclopentadienyl (Cp) ligand is of fundamental importance for organometallic chemistry and as such found in countless transition-metal catalysts. Chiral versions of these catalysts often employed tethering strategies to the complexed metal, which goes to the expense of free coordination sites. Our group has developed chiral versions of these ligands, which keep the maximum number of coordination sites unoccupied and therefore available in the catalytic cycle.[1]

Ruthenium catalyzed cycloisomerizations offer a rapid access to complex molecular frameworks in an atom economical fashion.[2] Therefore the cationic $[CpRu(MeCN)_3]PF_6$ complex found widespread application in organic synthesis. Recently we reported the synthesis of a set of chiral cationic Ru(II) catalysts bearing our chiral Cp^X ligands and their application in the formal [4+2] cyclization of yne-enones to the corresponding pyrans in high enantioselectivity.[3]



In the course of this project we discovered a considerably large influence of the counterion on the reactivity and selectivity of the transformation. We opted to explore these effects with particular emphasis on covalently binding anions, thus obtaining a chiral congener of the well-established neutral Cp*Ru(cod)Cl catalyst. This idea proved to be feasible and let to the development of an asymmetric version the Ruthenium catalyzed formal [2+2] reaction of strained bicyclic alkenes with internal alkynes to chiral *exo*-cyclic cyclobutenes.[4]



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Oligoprolines as a Versatile Platform for the Self-Assembly of π-Systems

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Incorporation of building blocks bearing specific functionality into larger entities has enormous potential for material science due to the possibility of bridging the gap between the molecular and macroscopic scale in terms of order, when precise control of the self-assembly process is achieved.[1,2] Efforts have been made to create well-ordered, functional structures based on DNA and polypeptide,. which can be easily decorated with the desired functionality. Until now the use of rigid peptidic scaffolds for such purposes has been limited.[3]

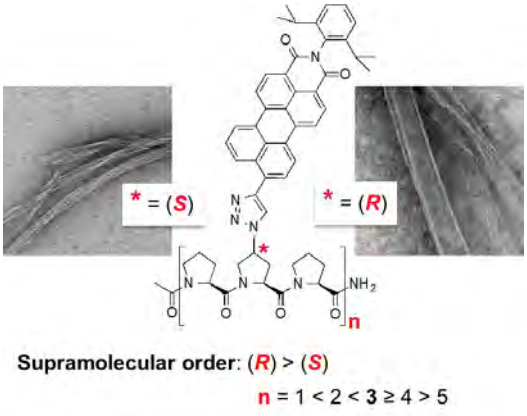

Figure 1. Molecular design of oligoproline-chromophore conjugates leading to distinct morphologies viewed by TEM.

Functionalizable, azidoproline-containing oligoprolines were chosen as scaffolds for the directed self-assembly of π-conjugated systems as they adopt already at a short chain lengths of six residues the conformationally well-defined polyproline II (PPII) helix, in which every third residue is stacked on top of each other in a distance of ~1 nm.[4] We have shown that both the length and the stereochemistry of the peptide backbone affect the supramolecular assembly of oligoproline–PMI conjugates significantly [5,6] and allowed for achieving hierarchical self-assembly of various chromophores from fibers, through nanosheets to well-defined hexagonal microcrystalline material (Figure 1). The aim of the project is to create and control nanostructured materials for the generation of ordered mesoscopic materials that could be applied in macroscopic organic electronic devices.

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Direct Ester to Arene Transformation

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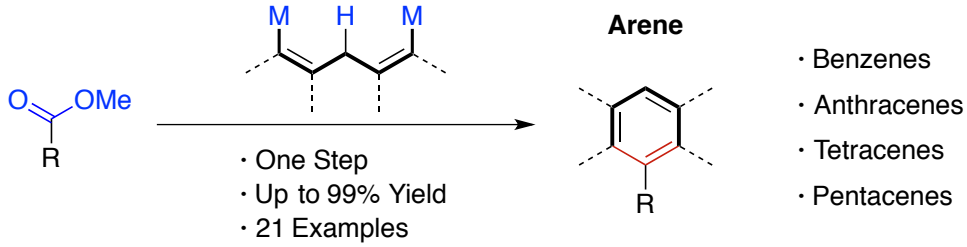
achim.link@unibas.ch

Carboxylic acid esters are ubiquitous intermediates in organic synthesis. A large and structurally distinct variety of this class of compounds is therefore available in almost every laboratory. On the other hand, arenes are privileged molecular scaffolds due to their stability, rigidity and the manifold use in functional or bioactive entities. While arenes are routinely prepared by transition metal catalyzed cross-coupling reactions using reaction specific substrates, a direct transformation of esters into arenes would give straightforward access to a striking number of high value products.

The poster will outline the first direct transformation of carboxylic acid esters into arenes by using 1,5-bifunctional organomagnesium reagents. These reagents were obtained by a two-fold iodine-magnesium exchange or by direct methods. Various esters were converted with these reagents to form the corresponding arenes in a one-step double addition, 1,4-elimination sequence, providing benzenes, anthracenes, tetracenes and pentacenes with up to 99% yield.



A. Link, C. Fischer, C. Sparr, *Angew. Chem.* **2015**, *127*, 12331–12334; *Angew. Chem. Int. Ed.* **2015**, *54*, 12163–12166.

Cosolvent fractionation of PMOXA-PDMS-PMOXA: bulk separation of triblocks from multiblocks

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The engineering of a broad range of bio-polymer hybrid systems is based on selfassembled polymeric membranes [1]. The self-assembly process of amphiphilic block copolymers into such membranes is influenced by many different factors, like polymer composition, temperature, method and time of polymersome formation. The cationic ring opening polymerization of 2-oxazolines is affected by chain transfer reactions [2], leading to the formation of multiblock copolymers which affect the self-assembly process negatively.

PMOXA-PDMS-PMOXA is one of the most widely used block copolymers for the assembly of polymersomes hosting membrane proteins such as OmpF to yield enzymatic nanoreactors [3]. Fundamental studies [4] and the broad range of applications [1] require functionalized and well-defined polymeric materials. Here, we present a new cosolvent extraction method to overcome the side products formed by chain transfer reactions during the 2-methyl-2-oxazoline polymerization as illustrated in Fig. 1.

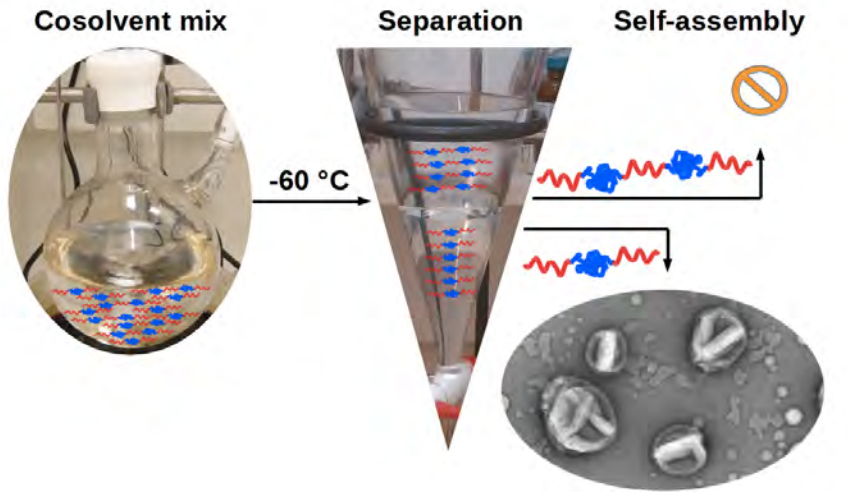

Figure 1. Schematic illustration of the cosolvent extraction enabling the separation polymersome forming triblock copolymers from multiblock copolymers.

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Stereoselective Arene-Forming Aldol Condensation: Synthesis of Configurationally Stable Oligo-1,2-naphthylenes

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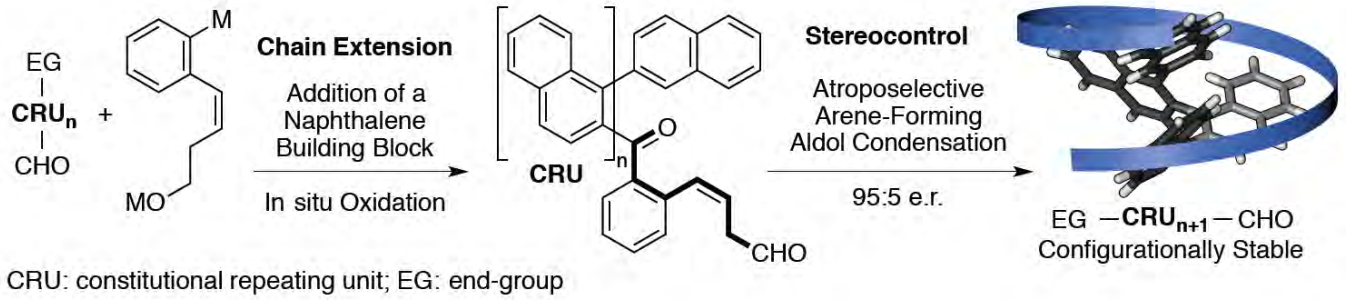
Structurally well-defined oligomers play a fundamental role in the function of natural systems, such as peptides or DNA. Synthetic counterparts, e.g. truncated helicenes, are often characterized by a low configurational stability and typically pose a substantial synthetic challenge.

The poster will outline our approach to the catalyst-controlled synthesis of oligo-1,2-naphthylenes. Based on the hindered rotation about the aryl-aryl single bonds, these oligomers show high configurational stability. For the efficient oligomer assembly, an building block addition approach was developed. An *in situ* double oxidation followed by a stereoselective arene-forming aldol condensation elongates the oligomer by one unit. The shape, such as the *P*-helix secondary structure is thereby transcribed from a chiral amine catalyst and excellent atropoenantio- and atropodiastereoselectivity of up to 95:5 was achieved.



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Use of keteniminium salts for the synthesis of strigolactones for crop enhancement applications, of small rings and of aromatic derivatives

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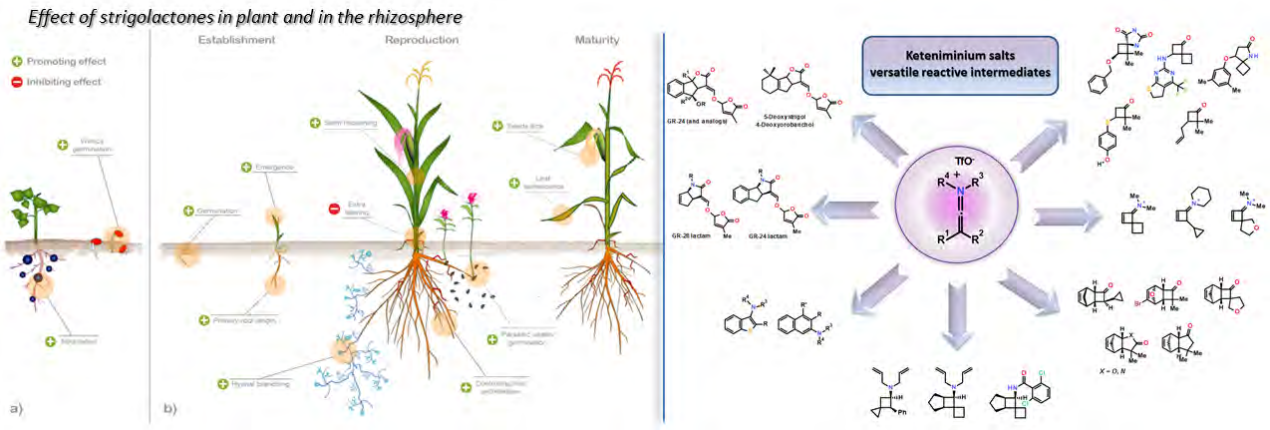
New technologies able to mitigate the main abiotic stresses (i.e. drought, salinity, cold and heat) represent a substantial opportunity to contribute to a sustainable increase of agricultural productions. In this context, the recently discovered phytohormone strigolactone is an important area of study which can underpin the quest for new anti-stress technologies.[1,2] The pleiotropic roles played by strigolactones in plant growth/development and in plant adaptation to environmental changes can pave the way for new innovative crop enhancement applications. In this context, we have developed a straighforward access to natural strigolactones and new potent synthetic analogs (strigolactams).[2]

Exploiting our experience in keteniminium chemistry, new accesses to functionalized small rings have been developed based on [2+2] cycloadditions between keteniminium salts and alkenes or alkynes which can be followed in the latter case by a Michael addition or a [4+2] cycloaddition reactions.[3,4,6] Methodologies to prepare functionalized amino-benzothiophene and naphtylamine derivatives have been also developed using a 6π- and 6π/10π -electrocyclization, respectively.[5]



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Radical-Mediated Enantioselective Hydroazidation of Alkenes

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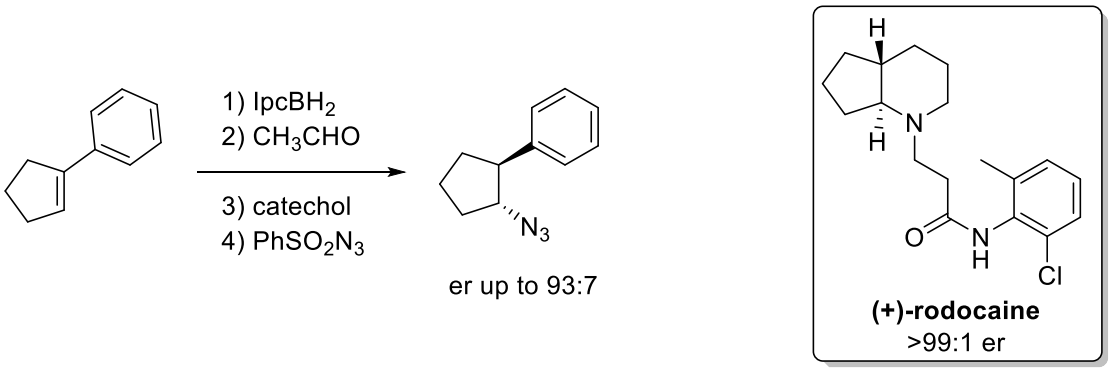
The formation of carbon-nitrogen bonds using organic azides as radical traps has attracted the attention of many different research groups. We recently described a radical procedure for the *anti*-Markovnikov hydroazidation using catecholborane as hydroboration agent followed by reaction with benzenesulfonyl azide as radical trap.[1] We developed now an enantioselective type of this reaction using isopinocampheylborane as chiral hydroboration agent.[2] This four-step-one-pot procedure includes the further conversion of the chiral alkylborane into the diethyl boronic ester,[3] transesterification to the alkylcatecholborane and final radical azidation.



In order to demonstrate the utility of the method, the first enantioselective synthesis of (+)-rodocaine was achieved.

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"Active Surfaces": Biomelecule - Polymer Membranes for Efficient Sensing of Phenols

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[b]Department of Product Design, Mechatronics and Environment, Transilvania Univ. of Brasov, 29 Eroilor Blv, 500036 Brasov, Romania

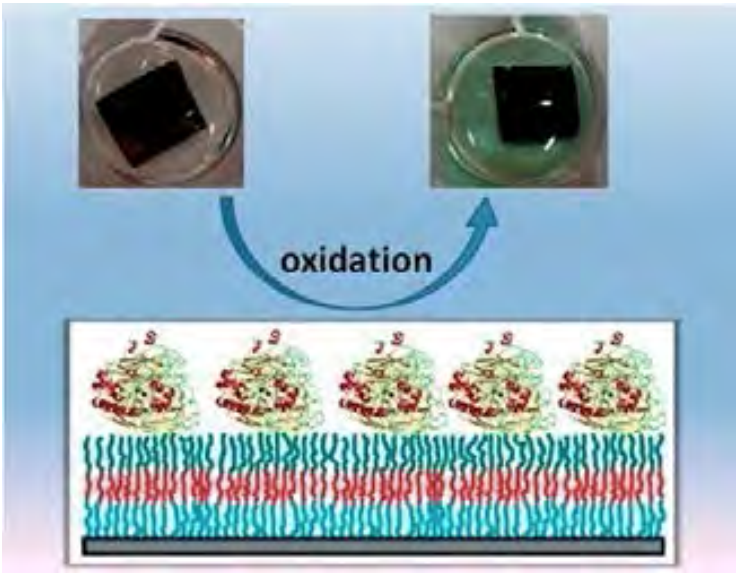

Figure 1: Oxidation of a phenolic compound by the active surface

The design of surfaces that present active compounds at the interface with their environment is on focus today in various domains, such as catalysis, medicine or environmental sciences. An elegant approach is to combine biomolecules (enzymes, proteins, mimics) with synthetic membranes in order to generate a stable and functional hybrid system.1

Here we present how two different enzymes are combined with asymmetric membranes and serve for development of "active surfaces" for sensitive detection of specific compounds. Solid supported membranes of PEG45-b-PMCLx-b-PDMAEMAy copolymers were prepared by LB-LS methods in different combinations of conditions. Laccase and Tyrosinase, as model enzymes for detection of phenol compounds were immobilized on soft surfaces resulting from polymer films deposition. Interestingly, the enzymes activity and stability varied depending on the film properties, which support further optimization of such active surfaces.

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Trialkylation of cyclic thioiminium ions

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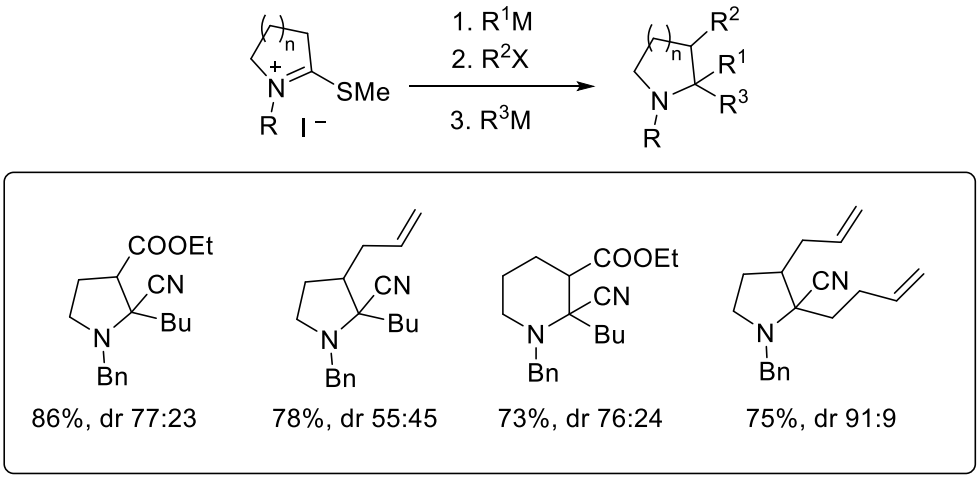
Thioiminium ions are excellent bis-electrophiles for the preparation of symmetrical *gem*-dialkylated cyclic amines. [1] More recently, we have developed the addition of organocopper reagents to thioiminium ions for the functionalization of the α-position of nitrogen atom, a method to prepare non-symmetrical *gem*-dialkylated cyclic amines. [2]
Here, we report an extension of this work, where a cyclic thioiminium ion is converted into trialkylated cyclic amines in a one-pot process via successive treatment with nucleophile (R^1M), an electrophile (R^2X) and a second nucleophile (R^3M). The scope and limitation of this reaction as well as its mechanism will be discussed.



Our transformation, in which 3 C-C bonds are formed in one single process will be used for the synthesis of alkaloid (±)-isoretronecanol.

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Exploring Shear-sensitive Liposomes

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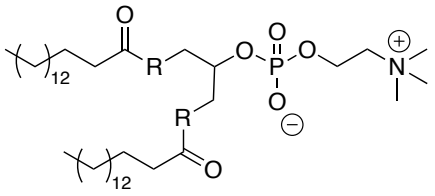
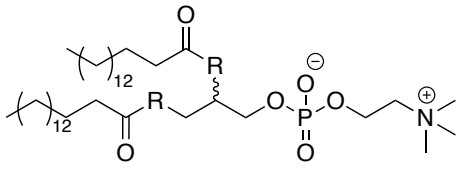
Liposomes of the artificial phospholipid Pad-PC-Pad (pictured below) show a surprisingly low complement activation related pseudo allergy response,[1] they are of lenticular shape and shear-sensitive.[1,2] These facetted liposomes release their cargo, when they are exposed to mechanical forces, whereas if they are at rest the embedded content remains inside the liposomes.[2] This mechano-sensitive behavior of the liposomes could be used as a novel trigger in targeted drug delivery.[3] Shear-stress differences in blocked arteries could then trigger the release of e.g. a vasodilator from liposomes for the acute treatment of myocardial infarction patients.



Pad-PC-Pad R = NH
Pes-PC-Pes R = O



Pad-Pad-PC R = NH
DPPC R = O

In order to understand the formation of facets and the mechano-sensitive behavior of Pad-PC-Pad vesicles, a library of phospholipids with and without hydrogen bond forming linkers, different tail lengths and with the natural 1,2-substitution pattern as well as the artificial 1,3-substitution pattern at the backbone were synthesized. Furthermore, release data were determined in order to understand which parameters in the lipids influence their mechano-sensitivity. From our observations, one can conclude that lipids with intramolecular hydrogen bonding form facetted d-formed[4] or cubic vesicles, whereas the ones without the ability to form hydrogen bonds present spherical liposomes. From the investigated lipids, Pad-PC-Pad is the most promising candidate for targeted drug delivery induced by shear-stress due to its high release under mechanical stress and its high stability over time.

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On the Mechanism of the Acid-Catalyzed Stereoselective Chroman Cyclization Reaction

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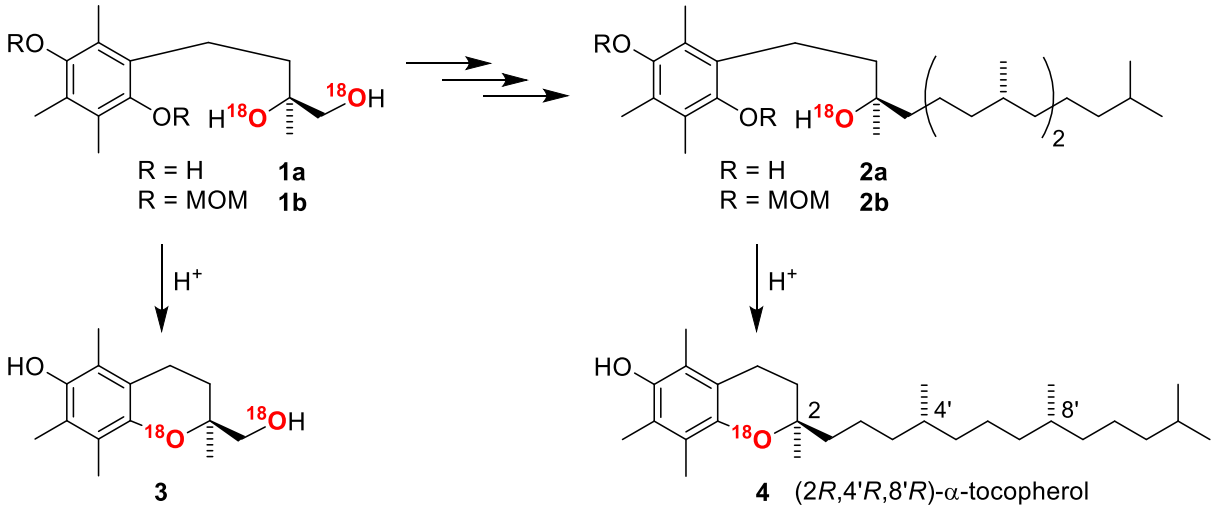
Naturally occurring tocopherols and tocotrienols are single-isomer vitamin E compounds. (2*R*,4'*R*,8'*R*)-α-Tocopherol (**4**) as a prominent example is of high commercial interest due to its biological and antioxidant properties.[1] Although the stereospecific cyclization reaction of intermediates and precursors such as **1a**/**2a** to chromans **3**/**4** under carefully controlled acidic conditions is known for a long time,[2] the mechanism of this transformation is unknown. This acid-catalyzed chroman cyclization has been used as a key step in many total syntheses,[3] and is of importance for larger-scale applications towards vitamin E and corresponding building blocks.



We investigated the course of the acid-catalyzed ring closure reaction by starting from doubly ^{18}O-labelled derivative **1b** (synthesized via stereoselective bishydroxylation). Chromans **3** and **4** (via intermediate **2b**) obtained by applying standard literature procedures showed complete (>95%) chirality transfer as well as ^{18}O-incorporation. The mechanism proposed will be discussed in comparison to findings documented in previous research papers.

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N-Heterocycles *via* Enantioselective Pd(0)-Catalysed C(sp^3)-H Functionalisation

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Nitrogen-containing heterocycles are prevalent motives in biologically active compounds.[1] In the past years, the enantioselective access to benzannulated *N*-heterocyclic building blocks *via* intramolecular Pd(0)-catalysed C-H arylation has been extensively investigated in our research group.[2]

Recently, we have expanded the scope of Pd(0)-catalysed C(sp^3)-H functionalisations beyond aryl halides. Readily accessible chloroacetamides are cyclized to valuable chiral β–[3] and γ–lactams[4] in high yields and enantioselectivities, bringing the elusive Pd(0)-catalysed C(sp^3)-C(sp^3) bond formation to a synthetically useful level.

Encouraged by the increasing interest in trifluoromethylated compounds for drug development, we have investigated the C(sp^3)-H functionalisation of trifluoroacetimidoyl chlorides, obtained in one step from the corresponding anilines. The efficient cyclisation under Pd(0)-catalysis does not require the use of stoichiometric trifluoromethylating reagents or protective groups, thus providing an economic strategy for the synthesis of 2-CF3-indoles.[5]

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O-Functionalized 1,2,3-Triazolylidene Metal Complexes for Redox Catalysis

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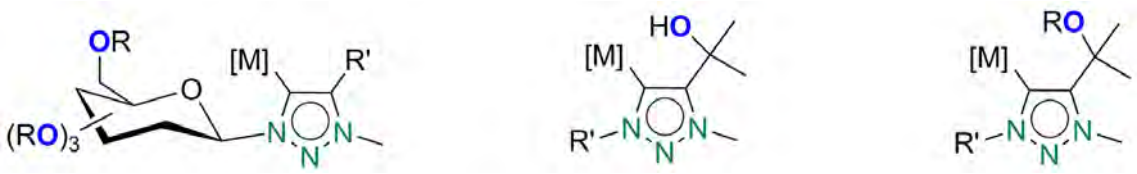
1,2,3-Triazolylidenes are a unique class of carbenes which have many advantages over classical N-heterocyclic carbenes (NHCs) including ease of synthesis and modification, and increased σ-donation properties.[1] Since *O*- and *N*-functionalization of classical NHCs has been shown to enhance the catalytic activity of the metal center, in particular for (transfer) hydrogenation reactions.[2,3] We aimed to explore the implication of such functional groups in combination with triazolylidene ligands. To this end, we have synthesized a range of metal complexes bearing *O*-functionalized 1,2,3-triazolylidene ligands. In this presentation, we will discuss the effects of this functional group, and the catalytic applications of the corresponding complexes in transfer hydrogenation and dehydrogenation reactions.



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Discovery and biological evaluation of PQR620, a highly potent and selective mTORC1/2 inhibitor

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The mammalian target of rapamycin (mTOR) signaling pathway plays a fundamental role in cell proliferation, differentiation, growth and survival.[1] Drugs targeting the mTOR signaling pathway represent a valuable path to address cancer therapeutic strategies.[2] Here, we report the lead optimization of PQR620, a novel potent and selective brain penetrant inhibitor of mTORC1/2.

The development of selective mTOR inhibitors is particularly challenging due to extensively conserved amino acid residues in the ATP binding pocket of PI3K and PI3K-related protein kinases. Here, we present a detailed ligand-based structure activity relationship study allowing selective targeting of mTOR kinase activity. Systematic variation of the hinge region and affinity binding motifs led to the identification of PQR620. Substitution of the morpholine binding to the hinge region and introduction of a 2-aminopyridine, substituted with a difluoromethyl group, induced a >1000-fold selectivity towards mTOR over PI3Kα in enzymatic binding assays.

In A2058 melanoma cells PQR620 demonstrated inhibition of protein kinase B (PKB, pSer473) and ribosomal protein S6 (pS6, pSer235/236) phosphorylation with IC_{50} values of 0.2 µM and 0.1 µM, respectively. PQR620 showed excellent selectivity over a wide panel of kinases, as well as excellent selectivity *versus* unrelated receptor enzymes and ion channels. Moreover, PQR620 demonstrated potency in a panel of 66 cancer cell lines (NTRC Oncolines™) to prevent cancer cell growth ($^{10}\log(IC_{50}, nM) = 2.86$, corresponding to an IC_{50} of 723 nM). The physico-chemical properties of PQR620 result in good oral bioavailability and excellent brain penetration. In mice and rats oral application of PQR620 exhibited a dose-proportional PK. Plasma to brain ratio was at least 1 and C_{max} was reached after 30 minutes.

PQR620 shows anti-tumor effects *in vivo* and is currently in pre-clinical development.

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Activity Improvement by Immobilization and Protection of Artificial Imine Reductase on Silica Nanoparticles

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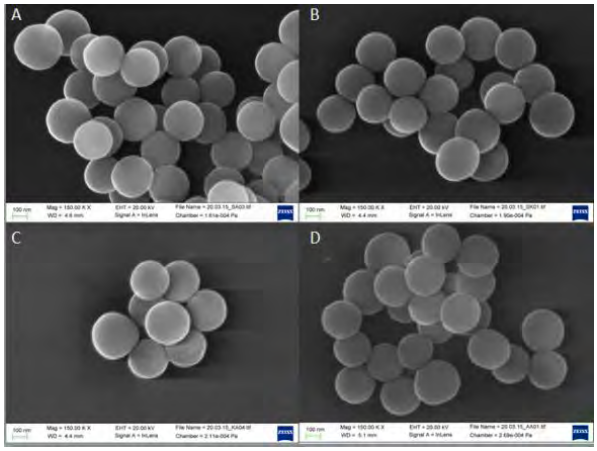
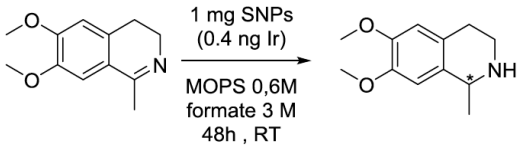
Artificial metalloenzymes (ArMs) are hybrid catalysts created by a non-covalent incorporation of an organometallic cofactor within a host protein scaffold.1,2 Such system based on the biotin-streptavidin technology combines organometallic and enzymatic catalysis,3,4 and can therefore catalyze multiple chemical processes. With the aim of immobilizing Artificial Transfer Hydrogenase (ATHase) on silica nanoparticles (SNPs) and performing NAD+ regeneration *in situ*, we selected the enantioselective transfer hydrogenation of cyclic imines as a model reaction.



Various lyophilized streptavidin isoforms were pre-incubated with the biotinylated iridium cofactor to obtain the functional artificial metalloenzymes, which were embedded within a protective organosilica layer 5 yielding active SNPs.



Upon immobilization and protection of streptavidin mutants on the SNPs, the resulting nanoparticles display increased TON (46'000)6 for the salsolidine precursor reduction, with the possibility to recycle the active catalyst. This protected system is able to retain its activity in presence of various cellular debris without any treating agent. The concentration of the active Cp*Ir catalyst was determined by means of ICP-MS measurements.

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Palladium-Catalyzed Long-Range Deconjugative Isomerization of Highly Substituted α,β-Unsaturated Carbonyl Compounds

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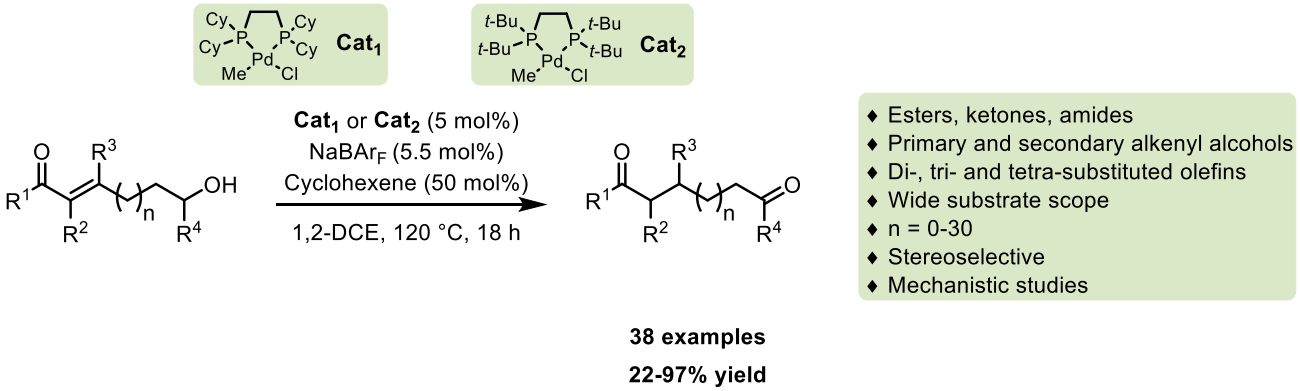
The long range isomerization/refunctionalization of olefins has emerged as an effective method for the construction of functionalized molecules starting from readily available precursors. This redox neutral methodology relies mostly on the use of transition metal complexes, with the economic and environmental advantage to avoid the formation of stoichiometric waste.[1] However, the main challenges for the successful development of such processes are (i) the difficult coordination of highly substituted (prochiral) olefins with metal catalysts,[2] severely narrowing the scope of these methodologies, and (ii) the control of the regioselectivity of metal hydride insertion across the C=C bond.[3]

Building on previous studies in our group,[4] we report herein the application of two Pd catalysts to the deconjugation, isomerization and refunctionalization of α,β-unsaturated carbonyls in good to high yields. Our system successfully isomerizes di-, tri- and tetra-substituted olefins to highly valuable aldehydes and ketones regardless the chain length (up to 38 examples). We also conducted mechanistic studies in order to understand the factors that govern such reaction. Preliminary results of the asymmetric variant of the reaction will also be presented.



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Fast antibacterial kinetics of metal oxides coated polymers

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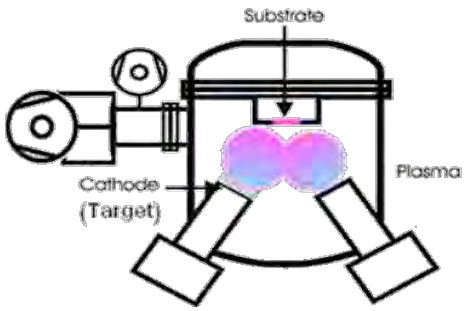
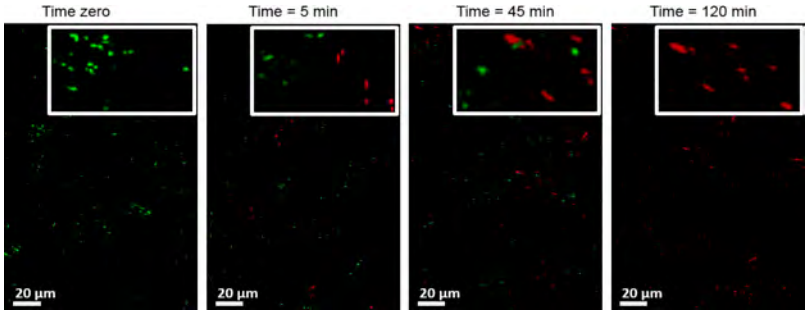
Compact uniform and adhesive TiO_2 deposited on thin polymer PE-films have been prepared by DC-magnetron sputtering (DCMS). TiO_2 sputtered on polyethylene (PE) showed effective and fast bacterial reduction kinetics and methylene blue (MB) self-cleaning properties under low intensity solar light [1-2].





During the bacterial inactivation, the shift in the vibrational peaks of the infrared -CH_2 bands was attributed to the increase in the -CH_2 bond stretching taking place preceding bond lysis and complete bacterial inactivation. The bacterial inactivation time was concomitant with the time required for the hydrophobic to hydrophilic transformation on PE-TiO_2 surface under band-gap irradiation [3]. The production of malondialdehyde (MDA) was observed during *E. coli* loss of viability.

The first evidence for Cu−Ag (50%/50%) nanoparticulate hybrid coatings is presented leading to a complete and almost instantaneous bacterial inactivation in the dark (≤5 min). Dark bacterial inactivation times on Cu−Ag (50%/50%) were observed to coincide with the times required by actinic light irradiation on 3D polyurethane catheters. This provides the evidence that the bimetal Cu-Ag driven inactivation predominates over a CuO/Cu_2O and Ag_2O oxides inducing a semiconductor driven behavior. Cu- or Ag-coated polyurethane catheters led to bacterial inactivation needing about ~30 min.

These PE-TiO_2 and other metals/metal oxides sputtered surfaces present a potential practical application for the disinfection since they preclude the formation of biofilms on PE, polyurethane and medical textiles [4-5].

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Contribution to the discovery of the biological mechanism of Buruli Ulcer thanks to a modular total synthesis

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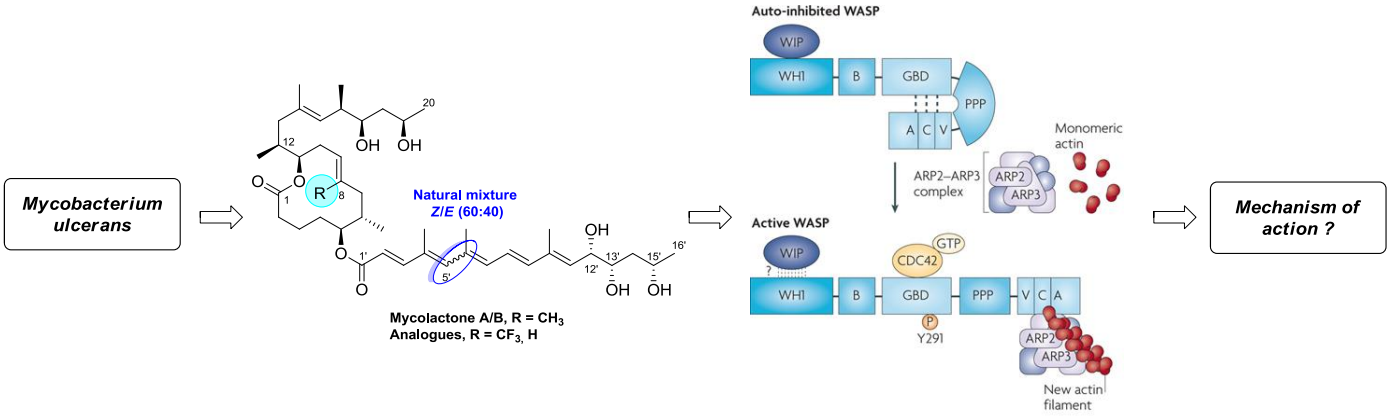
Buruli ulcer is a necrotizing skin disease present in more than thirty countries in the world, located mainly in West and Central Africa but also in Australia and in Japan.[1] This infection is caused by *Mycobacterium ulcerans* (*M. u.*) that secretes a macrolide toxin called mycolactone, which is the first polyketide isolated from a human pathogen. The disease is characterized by the formation of progressive necrotic lesions combined with a lack of acute inflammatory response, and mycolactone is known to be directly involved in the biological mechanism. Recently, two important regulators of the actin cytoskeleton, WASP and N-WASP, have been discovered as the first proteic targets of the toxin.[2-3]

To date no specific and efficient treatment of Buruli ulcer has been developed which correlates with the dramatic lack of understanding of the chemical and biological mechanisms connected to the disease. Moreover, the difficulty encountered by biologists to obtain this toxin from cultures of *M. u.*, led us to develop a diverted synthetic route for obtaining this toxin and its analogues with a high degree of purity in order to understand the onset of the disease.[4-5]



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Effect of supramolecular interactions in dendronized polymers on their thermal- and viscoelastic properties

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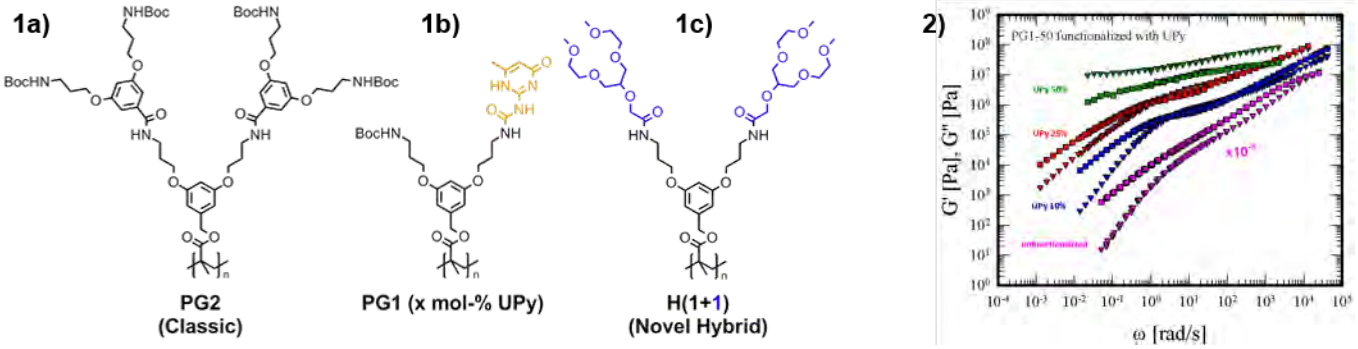
[1]ETH Zurich, [2]FORTH Heraklion, Greece, [3]University of Crete, Greece

Dendronized polymers (DPs) represent an intriguing class of macromolecules combining the concepts of dendrimers and polymers [1]. By tailoring their thickness and persistence length through the generation number (g) and backbone degree of polymerization (P_n), respectively, DPs can be endowed with a wide range of conformations, spanning from flexible polymers to shape-anisotropic colloidal objects.



In order to approach the intrinsic properties of these interesting materials, we performed modifications to our prototype "classic" DPs [2] (Fig. 1a) aimed at enhancing or suppressing their intermolecular hydrogen-bonding interactions through incorporation of strongly hydrogen-bonding ureidopyrimidinone (UPy) moieties (Fig. 1b) or hybridization with oligo(ethylene glycol)-based dendrons [3] (Fig. 1c), respectively. We present the effects of g = 1-3, various P_ns and chemical modifications on the thermomechanical properties of these novel DPs, which have been systematically investigated by DSC and rheology. The studied DPs undergo very slow ageing owing to the reduced global mobility of these bulky molecules. Even so, segmental mobility is increased in the hybrid DPs and constrained in the UPy DPs, which translates into vastly different equilibration times and glass transition temperatures. The very large entanglement molecular weight of the classic DPs causes a frequency dependent rheological response, which is typically characterized by low values of the entanglement plateau modulus in the low frequency regime, similarly to bottlebrush polymers but tuneable through both g and P_n. At it, UPy-functionalization broadens the scope of rheological responses even further (Fig. 2). Our results demonstrate remarkable effects of the chemical structure on the viscoelastic properties of such super soft elastomers with ultra-high molar mass and pave the way into exciting applications.

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Targeting the Colchicine-binding Site of Tubulin with 4-(pyrimidin-2-yl)morpholines

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Microtubule (MT) dynamics play a crucial role in the regulation of cellular motility, maintenance of cell shape, secretion, intercellular transport, and are indispensable for spindle formation during mitosis.[1] Small molecules interfering with MT dynamics have been recognized as valuable therapies in cancer.[2, 3]

A systematic structure-activity relationship (SAR) study starting from morpholino-substituted biheteroaryls with moderate microtubule disrupting activities allowed for the optimization of biological activity, metabolic stability, and drug-like properties. In this study, we focused on compounds with pyrimidine cores substituted with small *N*-heterocyclic moieties and identified compounds that potently inhibit cellular microtubule polymerization with EC_{50} values of 20-120 nM. Cellular activity was confirmed by monitoring phosphorylation of Histone H3, nuclear DNA condensation and mitotic cell cycle arrest across multiple cell lines. The compounds were shown to be poor substrates for P-gp multi-drug resistance pumps, and consequently efficiently caused mitotic arrest and cell death in colchicine resistant cells.

The co-crystal structure of tubulin with selected compounds showed that 4-(pyrimidin-2-yl)morpholines bind to the colchicine-binding site located between the α and β subunits of the αβ-tubulin dimer. Relevant inhibitor contact residues include Lys352, Met259, Ala316, Leu248, Val238, Tyr202 and Cys241 of β-tubulin. Moreover, two water molecules link the morpholine oxygen to the α -tubulin bound GTP. Conformational changes induced by inhibitor binding suggest that free or plus end tubulin is targeted by this compound series.

Pre-clinical studies characterized a lead compound selection with excellent stability in human hepatocytes, and human, mouse and rat microsomes. Overall, these compounds qualify as a novel class of microtubule destabilizing agents that target the colchicine-binding site, and which warrant further development.

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Metal-free [2+2+2] cycloaddition of alkynes and nitriles for the construction of pyridine cores

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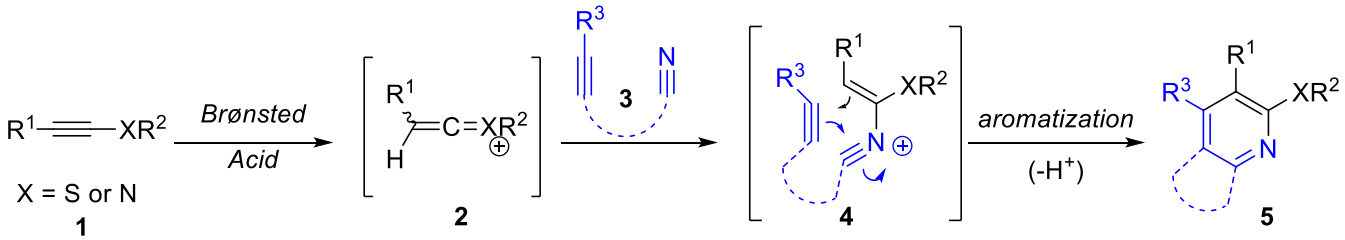
Among the heteroaromatic structures, pyridine plays a central role in the pharmaceutical industry.[1] Over the past decade, a number of synthetic strategies have been documented along with investigations focusing on transition metal- and organocatalysts.[2] Comparing with these strategies, [2+2+2] cycloaddition of simple alkynes and a nitrile offers an efficient, highly atom-economical, straightforward tool to access complex pyridine building blocks.[3] Nevertheless, strategies for pyridine construction by metal-free [2+2+2] cycloaddition are scarce.[4] We envisioned that an alkynyl-nitrile **3** might intercept a stabilized vinyl cation **2**, generated in situ by the addition of TfOH to an electron-rich alkyne **1**.This should form a tethered intermediate **4** in situ, which would be prone to cycloaddition leading to the corresponding pyridine product **5**. This protocol would offer us a me tal-free, formal intermolecular [2+2+2] cycloaddition to form substituted pyridine cores.[5]



Scheme 1. Proposed metal free [2+2+2] cycloaddition to generate pyridines.

Herein, we present our results on this novel methodology. The modularity and simplicity of the reagents, combined with the mild reaction conditions and low temperatures conspire to make this an appealing method for the rapid assembly of substituted pyridine structures.[5]

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Stereoselective Synthesis of Fluorinated Heterocycles Using Hydroformylation

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Stereoselective synthesis of fluorinated heterocyclic compounds is an active area of research with many applications in the synthesis of bioactive compounds.[1]

In this poster we will discuss a combination of enzymatic resolution and hydroformylation to access some heterocyclic fluorinated scaffolds in a straightforward manner. Finally, the transformation of one of the chiral building blocks into a novel and potentially useful agrochemical intermediate will be described.

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Well-Defined Water-soluble Fullerene-PVP Conjugate for PDT Application

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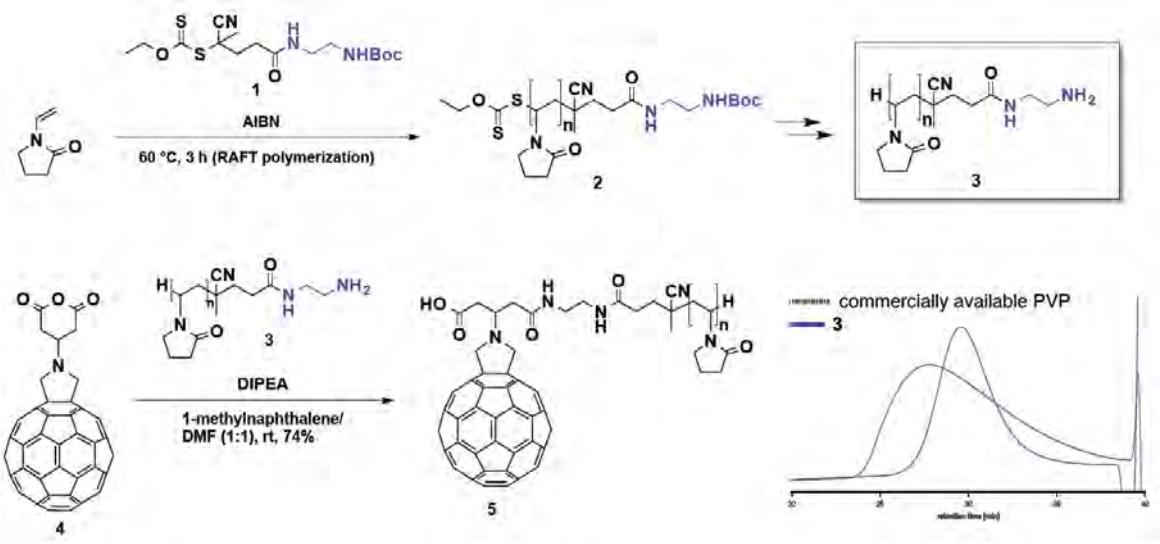
The potential medical application of highly photosensitive fullerenes (C_{60} and C_{70}) as photodynamic therapy (PDT) agents has been discussed for decades. Many methods to solubilize fullerenes in water or water-miscible solvents are being studied for the bioapplication of fullerenes. We have used a biocompatible and water-soluble polymer, poly(vinylpyrrolidone) (PVP), to prepare water-soluble C_{60}/ or C_{70}/PVP complexes[1] and C_{60}- or C_{70}-PVP conjugates[2]. [3] which can generate reactive oxygen species (ROSs) under visible light in high quantum yields.[4,5]

For clinical use, well-defined compounds with narrower molecular weight distribution are generally favored. In this study, we designed a RAFT reagent **1** for the preparation of well-defined PVP. Controlled polymerization of NVP in the presence of **1** successfully provided PVP **2**. The terminal moiety of **2** was converted to an amine **3** with molecular weight of around 20 kDa and a PDI of 1.29, which was available for the conjugation to C_{60} acid anhydride derivative **4**.[6] Obtained C_{60}-PVP conjugate showed a narrow molecular distribution (PDI = 1.31) with high water-solubility and ROS generation under visible light irradiation.[7]



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α-*C*-Glycosides *via syn* Opening of 1,2-Anhydro Sugars with Organozinc Compounds in Toluene/*n*-Bu_2O

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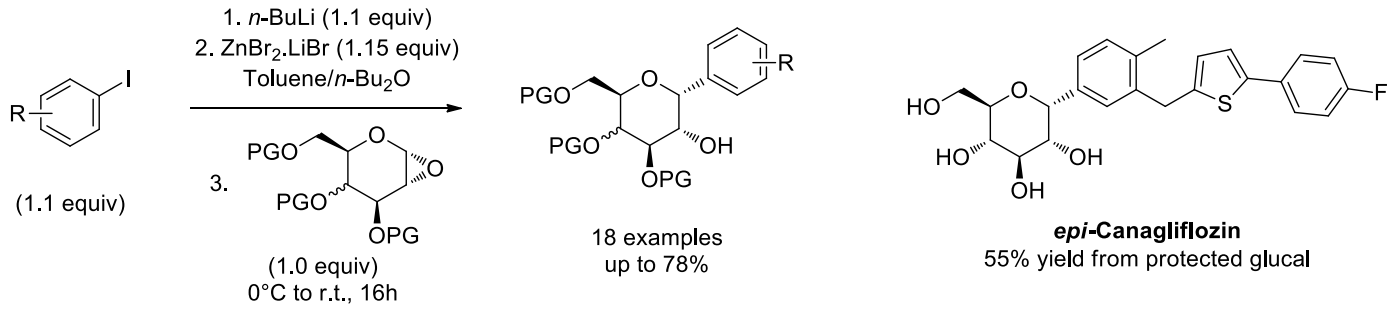
The diastereoselective addition of organozinc species to 1,2-anhydro sugars in toluene/*n*-dibutyl ether solvent is reported.[1] Compared to the existing methods, the reaction proceeds at 0°C and only a slight excess of nucleophile is required to achieve good yields. Scope was assessed with different *O*-protected glycals along with various nucleophiles (aryl, alkynyl). This methodology was applied to the synthesis of the -anomer of Canagliflozin.



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Kinetic Models of Cyclosporin A and Cyclosporin E to Rationalize Membrane Permeability

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The membrane permeability of cyclic peptides is strongly influenced by the conformational behaviour in polar and apolar environments. The size and complexity of peptides often limits their bioavailability, but there are known examples of peptide natural products that can cross cell membranes by passive diffusion. One of them is Cyclosporin A (CsA), used as a drug preventing transplant rejection [1]. CsA is an undecapeptide with seven methylated backbone amides. Its synthetic derivative, Cyclosporin E (CsE), lacks Val-11 *N*-methylation and its membrane permeability is one order of magnitude lower [2].

The aim of presented work is to rationalize the structural and kinetic differences between CsA and CsE leading to different permeability, using molecular dynamics simulations and Markov state models. Computational results are compared to experimental NMR data. The results suggest that the membrane permeability of cyclic peptide is connected to its ability to form "congruent" conformational states, i.e. conformational states significantly populated both in polar and apolar environments [3]. These findings should provide insights for the rational design of novel cyclic peptides for pharmaceutical industry.

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Palladium(0)-Catalyzed Asymmetric C(sp^3)–H Arylation: the Chiral Base Approach

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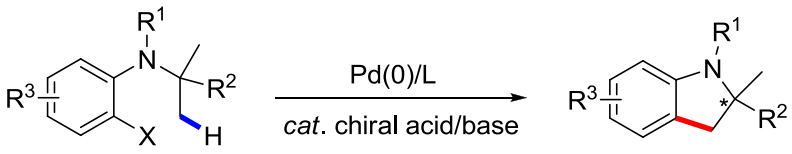
In recent years, transition-metal-catalyzed asymmetric C(sp^3)–H activation has received increasing attention.[1] ,[2] Kagan,[3] and Cramer[4] reported the highly enantioselective construction of (fused) indolines using chiral *N*-heterocyclic carbene or phosphine ligands. In parallel, our group has reported the diastereo- and enantioselective synthesis of (fused) indanes containing up to three adjacent stereocenters by using chiral Binepine ligands.[5] Herein, we show that the enantioselective synthesis of chiral indolines containing 2^{ary} and 3^{ary} stereocenters (up to 98:2 e.r.) can be achieved *via* C(sp^3)–H activation using a catalytic chiral base, which is formed in situ upon deprotonation of a chiral acid, as the sole source of chirality.[6]



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Terminal-selective functionalization of alkyl chains by regioconvergent cross-coupling

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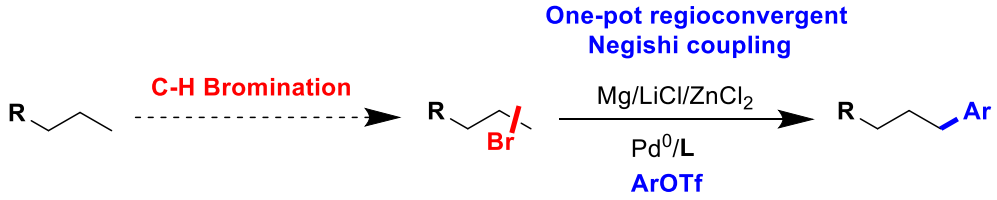
Palladium-catalyzed $C(sp^2)$-$C(sp^3)$ cross-couplings are particularly valuable tools in synthetic chemistry and hence a great deal of interest has emerged in this area.[1] Recently, our group has developed a new cross-coupling strategy based on the migration of an organopalladium species along an alkyl chain.[2] Through experimental and theoretical mechanistic studies, we have shown that this migration occurs through a β-H elimination/rotation/insertion sequence.[3]

In this work, we have extended this migrative-coupling to simple and commercially available alkyl bromides. Under practical Barbier-type conditions involving magnesium insertion and transmetallation with $ZnCl_2$, a series of linear arylated products could be obtained in a regioconvergent manner with good to excellent linear/branched selectivities, thanks to the use of a flexible phosphine ligand. Moreover, this strategy could be coupled to a non-selective radical bromination process, which allowed the functionalization of simple alkanes in just two steps.[4]



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Palladium-Catalyzed Enantioselective Intermolecular Carboetherification of Dihydrofurans

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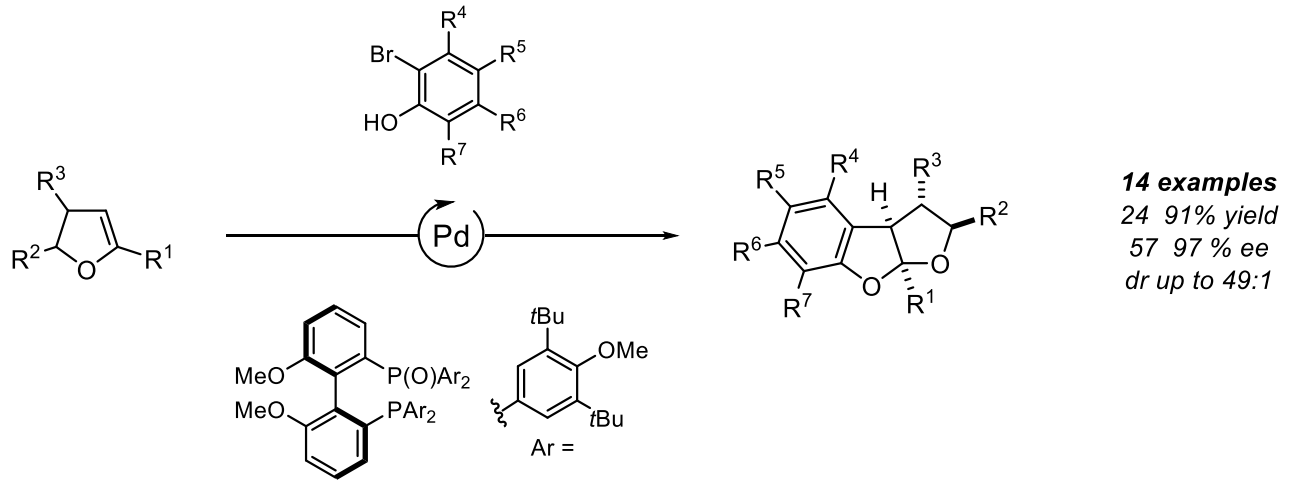
In recent years, efforts have been focused on the development of new methodologies for carbon-heteroatom bond formation,[1] owing to the ubiquity of aryl C-N and C-O bonds in agrochemicals, pharmaceuticals and natural products. Among these methodologies, the Pd-catalyzed carboetherification of alkenes has emerged as a powerful strategy. Despite remarkable advances in the field, most reported examples proceed via intramolecular reactions and their enantioselective variants are still scarce.[2,3]

Herein we describe a novel intermolecular carboetherification that gives direct access to fused tetrahydrofurobenzofurans; a scaffold that can be found in numerous biologically active compounds and which is tipically accesible via long and unpractical synthetic routes.[4] Under optimized conditions and using readily available starting materials, the final cross-coupling products are systematically obtained in high yield, enantio- and diastereoselectivity.[5] A key feature of our methodology is the *in situ* formation of a chiral bisphosphine mono-oxide (BPMO).



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