doi:10.2533/chimia.2012.570 Chimia 66 (2012) 570–605 © Schweizerische Chemische Gesellschaft

Organic Chemistry, Talk **358**

Screening of Chiral Organocatalysts for the Aldol Reaction by Mass Spectrometric Monitoring of the *Retro* Reaction

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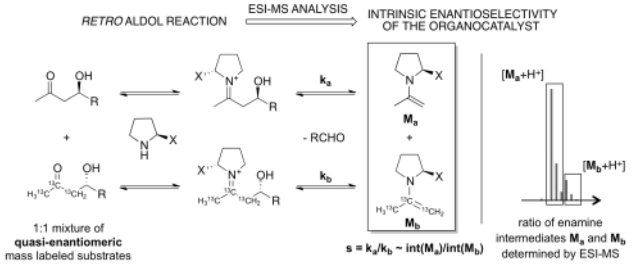
Recently, our group developed a new high throughput screening method for the determination of the intrinsic enantioselectivity of chiral catalysts for the Pd-catalyzed allylic substitution based on electrospray mass spectrometry and mass-labeled quasi-enantiomeric substrates [1]. As well, this method was successfully applied to organocatalyzed asymmetric Diels-Alder [2] and Michael reactions [3]. Monitoring the back reaction, the ratio of the detected intermediates reflects the enantioselectivity of the corresponding forward reaction.

Herein, we present our results for the application of this method to organocatalyzed aldol reactions. In contrast to our previous studies in which the iminium ion was the intermediate for ESI-MS analysis, the adol reactions proceed *via* enamines which are more challenging to visualize.



[1] For a review see: C. Müller, C. Markert, A. Teichert, A. Pfaltz, *Chem. Commun.* **2009**, 1607.
[2] A. Teichert, A. Pfaltz, *Angew. Chem. Int. Ed.* **2008**, *47*, 3360.
[3] I. Fleischer, A. Pfaltz, *Chem. Eur. J.* **2010**, *16*, 95.

Organic Chemistry, Talk **359**

A Concise Organocatalytic Approach for the Stereoselective Formal Synthesis of Anachelin H

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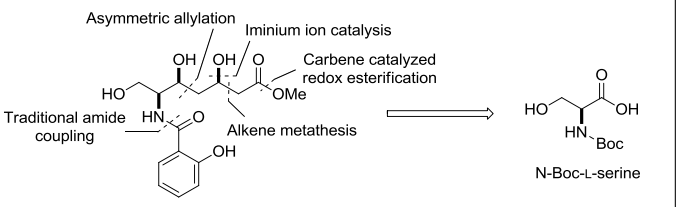
Department of Chemistry, University of Basel, St. Johanns-Ring 19, CH-4056 Basel, Switzerland

The iron chelator anachelin[1] is an important secondary metabolite for cyanobacteria *Anabaena cylindrica* exhibiting dual role of both self-growth acceleration and growth inhibition of competing green algae. Thus we decided to investigate the specific bioactivity of different fragments to get a clear insight into the dual mode of action of the complex natural product. Herein we present a concise route for the asymmetric synthesis of polyketide chain fragment. Starting from *N*-Boc-L-serine the synthesis comprises metal catalyzed asymmetric allylation on Garner aldehyde followed by Grubbs metathesis. The crucial part of the synthesis is the one-pot organocatalytic epoxidation and a follow-up esterification by a carbene catalyzed internal redox process.[2] Finally amidation and removal of protecting groups complete the stereoselective formal synthesis of this metabolite.



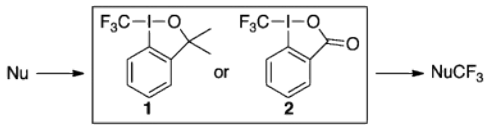
[1] K. Gademann, Y. Bethuel, *Org. Lett.* **2004**, *6*, 4707; K. Gademann, Y. Bethuel, *Angew. Chem. Int. Ed.* **2004**, *43*, 3327.
[2] H. Jiang, B. Gschwend, L. Albrecht, K. A. Jørgensen, *Org. Lett.* **2010**, *12*, 5052.

Organic Chemistry, Talk **360**

Mechanistic Insights into Electrophilic Trifluoromethylations with Hypervalent Iodine Reagents

N. Santschi, N. Hauser, A. Togni*

Department of Chemistry and Applied Biosciences, Swiss Federal Institute of Technology, ETH Zürich, CH-8093 Zürich, Switzerland



Since the advent of reagent **1** and **2** a plethora of nucleophiles have been successfully targeted. Among the first functional groups to be trifluoromethylated, thiols were the most promising ones due to short reaction times and a high functional group tolerance.[1]

When comparing the reactivity of chalcogens towards the reagents very different mechanistic behavior is observed. For example, hard oxygen nucleophiles such as hydrogen phosphates putatively form a complex through coordination to the iodonium core followed by reductive elimination to furnish the product.[2] Thiols, on the other hand, display distinct characteristics of a radical mechanism where the S-C bond formation event is proposed to occur through subsequent single electron transfers in a S_N2 type fashion. As a fundamental understanding of these mechanisms of action are important in order to specifically design new nucleophiles and improve on the reactivity of **1** and **2**, these differences will be discussed and experimental data corroborating either hypothesis presented.

[1] Kieltsch, I.; Eisenberger, P.; Togni, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 754.
[2] Santschi, N.; Geissbühler, P.; Togni, A. *J. Fluorine Chem.* **2012**, *135*, 83.

Organic Chemistry, Talk **361**

Chemical Protein Synthesis using α-Ketoacid–Hydroxylamine (KAHA) Ligation with 5-Oxaproline

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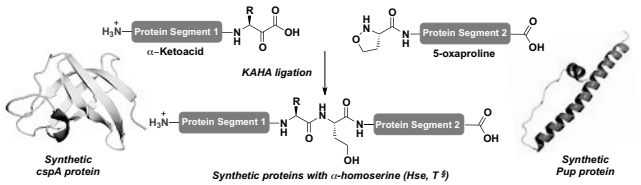
Laboratorium für Organische Chemie, Wolfgang-Pauli-Strasse 10, ETH Zürich, 8093 Switzerland

Chemoselective ligation reactions that can be performed in aqueous buffers with unprotected peptide/protein segments, ideally between any pair of amino acids, are valued reactions for chemical synthesis of proteins. The α-ketoacid–hydroxylamine (KAHA) ligation with 5-oxaproline is a promising method for the preparation of both natural and modified proteins. In this ligation, a C-terminal peptide α-ketoacid reacts chemoselectively with an N-terminal 5-oxaproline peptide to give the target protein with an α-homoserine at the ligation site. This ligation works well for the synthesis of proteins in aqueous buffers with unprotected protein segments and produces carbondioxide as the only by-product.



The synthesis of Prokaryotic ubiquitin-like protein (Pup) and probable cold-shock protein A (cspA) using KAHA ligation with 5-oxaproline will be discussed along with the scope of the ligation reaction.

[1] J. W. Bode, R. M. Fox, K. D. Baucom. *Angew. Chem. Int. Ed.* **2006**, *45*, 1248.
[2] V. R. Pattabiraman, A. O. Ogunkoya, J. W. Bode. *Angew. Chem. Int. Ed.* **2012**, DOI: 10.1002/anie.201200907.

Organic Chemistry, Talk **362**

Synthesis and biochemical characterization of triphosphates with side chains capable of organocatalysis and transition metal binding

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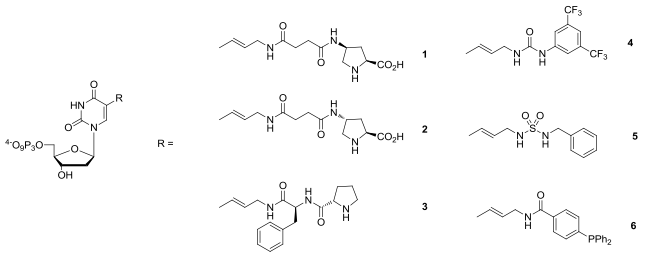
Nucleoside triphosphates (dNTPs) have advanced as a versatile platform for the generation of modified nucleic acids and a viable alternative to the traditional automated solid-phase synthesis of oligonucleotides [1]. Various dNTPs embellished with side-chains capable of enamine-based organocatalysis (**1**-**3**), activation of Lewis basic substrates through the casting of extended hydrogen bond networks (**4** and **5**), and binding to transition metals *via* phosphane lignads (**6**) were synthesized [2], [3].



The capacity of these modified dNTPs to act as substrates for DNA polymerases in particular, and their compatibility with SELEX in general, was also assessed.

[1] M. Hocek, M. Fojta, *Org. Biomol. Chem.* **2008**, *6*, 2233.
[2] M. Hollenstein, *Chimia*, **2011**, *65*, 770-775.
[3] M. Hollenstein, C. J. Leumann, *Chem. Eur. J.* **2012**, submitted.

Organic Chemistry, Talk **363**

Pd-Catalyzed Oxy- and Amino- Alkynylation of Olefins

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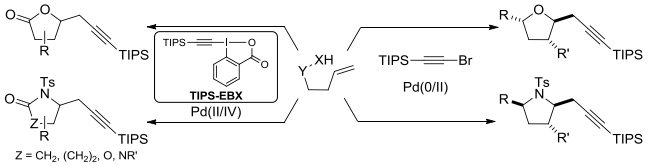
O- and *N*-containing heterocycles are common scaffolds in both natural products and other bioactive compounds. A valuable strategy for the synthesis of these compounds is based on the cyclization of *O*- and *N*-nucleophiles onto non-activated olefins combined with a further C-C bond forming event. Despite the enormous synthetic potential of acetylenes, no methods for the oxy- and aminoalkynylation of olefins had been previously described.

We report herein two complementary approaches based on Pd catalysis to achieve this kind of transformation. The cyclization of γ-alkenyl carboxylic acids[1] and *N*-tosyl amides[2] was effectively accomplished through a Pd(II/IV)-catalyzed process using the hypervalent iodine reagent TIPS-EBX. The γ- and δ- lactams accessed this way could be then used for the two-step synthesis of pyrrolizidine and indolizidine heterocycles. By contrast, 2-propargyl tetrahydrofurans and pyrrolidines could be obtained in excellent yields and diastereoselectivity by Pd(0/II)-catalyzed cyclization of alkenyl alcohols and amines using TIPS-protected bromoacetylene.



[1] Nicolai, S.; Erard, S.; Fernández-González, D; Waser, J. *Org. Lett.*, **2010**, *12*, 384.
[2] Nicolai, S.; Piemontesi, C.; Waser, J. *Angew. Chem Int. Ed.* **2011**, *51*, 4680.
[3] Nicolai, S.; Waser, J. *Org. Lett.* **2011**, *13*, 6324.

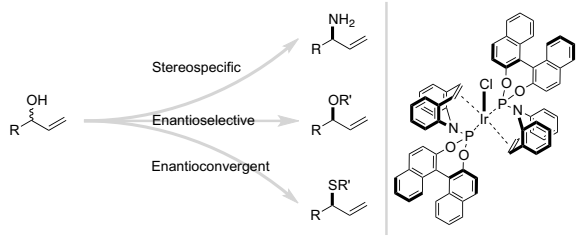
Organic Chemistry, Talk **364**

Enantioselective Allylic Amination, Etherification and Thioetherification with an uniquely reactive (P,alkene)-Ir Complex: Direct Substitution of racemic Allylic Alcohols

Markus Roggen, Erick M. Carreira

ETH Zürich, CH-8093 Zürich, Switzerland

Chiral allylic amines, ethers and thioethers are valuable intermediates in organic synthesis.



The reported iridium/phosphorous-olefin complex allows the direct conversion of branched allylic alcohols into various chiral products. Enantioselective[1] and enantiospecific[2] allylic amination uses sulfamic acid as a convenient ammonia surrogate. Enantioselective allylic etherification was achieved through the identification of a Brønsted acid promoter.[3] The catalyst tolerates thiols which enabled the development of an enantioselective allylic thioetherification, which was procedeeds via an unusual enantioconvergent mechanism, promoted by dibutyl phosphate.[4]

[1] C. Defieber, M. A. Ariger, P. Moriel, E. M. Carreira, *Angew. Chem. Int. Ed.* **2007**, *46*, 3139; b) M. Lafrance, M. Roggen, E. M. Carreira, *Angew. Chem. Int. Ed.* **2012**, *51*, 3470
[2] M. Roggen, E. M. Carreira, *J. Am. Chem. Soc.* **2010**, *132*, 11917.
[3] M. Roggen, E. M. Carreira, *Angew. Chem. Int. Ed.* **2011**, *50*, 5568.
[4] M. Roggen, E. M. Carreira, **2012**, *submitted*

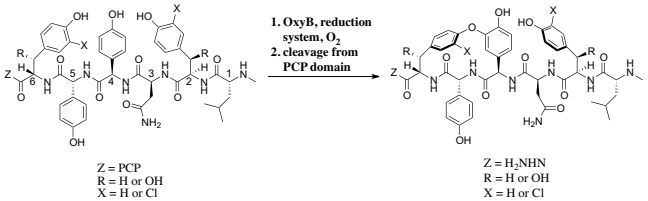
Organic Chemistry, Talk **365**

***In vitro* Studies on the Phenol Coupling and Aromatic Chlorination Reactions in Vancomycin Biosynthesis**

Patrick C. Schmartz, K. Zerbe, E. Gad, K. Abou-Hadeed, J. A. Robinson*

University of Zurich, Winterthurerstr. 190, CH-8057 Zurich, Switzerland

Glycopeptide antibiotics are promising candidates in the development of novel antibacterial compounds that retain activity against Gram-positive bacteria. Striking features of this class of natural products are the extensive phenol coupling of a linear peptidic precursor catalyzed by dedicated P450 enzymes and the regiospecific aromatic chlorination catalyzed by a single flavin-dependent halogenase. We have shown in previous substrate specificity studies with the vancomycin biosynthetic enzyme OxyB, which forms the first cross-link between residues-4 and -6, that this phenol coupling reaction can occur on a peptide carrier protein (PCP)-linked model hexapeptide including tyrosine in positions-2 and -6 [1]. The natural substrate of OxyB, however, should contain β-hydroxy groups in these residues. The exact timing of aromatic chlorination during non-ribosomal backbone assembly remains unproven (before or after phenol coupling). Here, we present an efficient method to investigate the effect of β-hydroxy groups and chlorine substituents in residues-2 and -6 on the OxyB catalyzed phenol coupling [2].



[1] K. Woithe *et al*., *J. Am. Chem. Soc*. **2007**, *129*, 6887-6895.
[2] P. C. Schmartz *et al*., manuscript submitted, **2012**.

Organic Chemistry, Talk **366**

Post CA-CR Transformations of PCBDs

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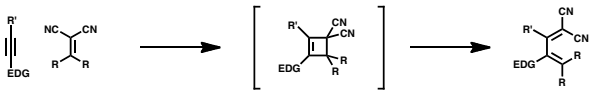
[1]Laboratorium für Organische Chemie, ETH Hönggerberg, HCI, CH-8093, Zürich, Switzerland
[2]Laboratoire d'Electrochemie et de Chimie Physique de Corps Solide, Institute de Chemie-LC3-UMR 7177, CNRS, Universitié Louis Pasteur, 4, rue de Blaise Pascal, F-67000 Strasbourg, France

The click-type cycloaddition cycloreversion (CA-CR) reaction between electron-rich alkynes, and polycyanoethenes [1] has been employed extensively for the rapid formation of poly-cyano butadienes (PCBDs) bearing electron donating substituents[2].



EDG = Electron Donating Group

We report herein that the application of an aniline functionality as the electron donor in the CA-CR reaction furnishes a flexible platform for subsequent transformations of PCBDs. Hence, for the first time, derivatives of this important class of compounds lacking an electron donating substituent have been prepared, and their electron reduction potentials have been assessed experiementally.

It has also been found that this novel class of PCBDs are stable to a wide range of reaction conditions, thus offering novel strategies for the introduction of this important motif into interesting scaffolds such as macrocycles and foldamers.

[1] T. Michinobu, J. C. May, J. H. Lim, C. Boudon, J. -P. Gisselbrecht, P. Seiler, M. Gross, I. Biaggio, F. Diederich, *Chem. Commun.* **2005**, 737.
[2] M. Kivala, F. Diederich, *Acc. Chem. Res.* **2009**, *42*, 235.

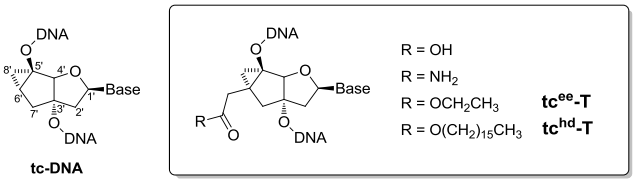
Organic Chemistry, Talk **367**

Synthesis of C(6')-functionalized tricyclo-DNA for the preparation of an oligonucleotide prodrug

Jory Liétard and Christian J. Leumann

Department of Chemistry and Biochemistry, University of Bern, Freiestrasse 3, 3012 Bern, Switzerland

Tricyclo-DNA (tc-DNA) is an oligonucleotide analog with therapeutic potential as antisense and siRNA agent. Indeed, tc-DNA binds to RNA with increased affinity, is resistant to nucleases and does not elicit RNase H-mediated cleavage.[1] However, as most of the other oligonucleotide analogs, tc-DNA suffers from poor cellular uptake. To address this issue, a promising strategy consists in temporarily introducing functional groups with biolabile moieties that are expected to be cleaved by cytosolic enzymes once the oligonucleotide is internalized (prodrug approach).[2] Therefore, in an attempt to prepare a tc-DNA prodrug, we modified the tricyclic sugar structure with a biolabile ester function at position C(6'). We report on the synthesis of C(6')-functionalized tc-DNA analogs as well as their incorporation into oligonucleotides. The biophysical properties of the modified oligonucleotides were investigated. A decathymidylate containing five lipophilic ester side chains (tc^{hd}-T) was shown to enter cells without the use of any transfection agent.



[1] Leumann, C. J. *Bioorg. Med. Chem.* **2002**, *10*, 841.
[2] Tosquellas, G.; Alvarez, K.; Dell'Aquila, C.; Morvan, F.; Vasseur, J.-J.; Imbach, J.-L.; Rayner, B. *Nucleic Acids Res.* **1998**, *26*, 2069.

Organic Chemistry, Talk **368**

Towards the Synthesis of Substituted Cycloparaphenylenes

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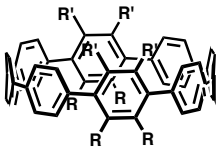
[1]University of Basel, St. Johanns-Ring 19, CH-4056 Basel, Switzerland.

Strained aromatic macrocycles have attracted the attention of chemist for over 80 years.[1] Recently the interest in cycloparaphenylene (CPP) increased dramatically as they can be viewed as the shortest fragment of an armchair carbon nanotube. The development of an efficient entry into these compounds might allow the controlled preparation of carbon nanotubes from a (CPP) precursor. In 2008, Bertozzi [2] presented the first synthesis of a CPP. Since then other groups contributed to this endeavor.[3] A modified approach, allowing the introduction of substituents at a late stage of the synthesis, was applied in this work. Differently substituted CPPs were successfully prepared. Such substituted CPPs will allow to further increase the understanding of this interesting class of molecules as well as further chemistry towards larger carbon nanotube fragments.



R, R' = Ph, Alk, CH_2OH

[1] Tahara, K.; Tobe, Y., *Chem. Rev.,* **2006,** *106*, 5274.
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[3] For a recent review see: Sisto T. J.; Jasti, R.; *Synlett.* **2012**, *23*, 483.

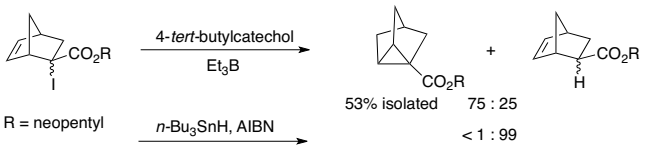
Organic Chemistry, Talk **369**

Polar Effects in Hydrogen Atom Transfers from Catechols to Alkyl Radicals

Guillaume Povie, Davide Pozzi, Giorgio Villa, Leigh Ford and Philippe Renaud

Universität Bern, Departement für Chemie und Biochemie, Freiestrasse 3, CH-3012 Bern, Switzerland

In combination with organoboranes, 4-*tert*-butylcatechol can be used as an efficient hydrogen atom donor in radical chain reactions.[1] This surprising behavior of a class of compounds generally seen as chain breaking antioxydants allowed the development of a broad scope method for the reduction of organoboranes.[2] Extending this concept to the reduction of alkyl iodides, the hydrogen atom transfer step was found to be particularly sensitive to the polarity of the attacking radical. While alkyl substituted radicals are efficiently reduced, electron poor radicals slowly react with catechol derivatives giving them sufficient lifetime to undergo addition reactions.



This peculiar feature could be used to trigger inter and intramolecular processes such as the contrathermodynamic 3-*exo-trig* cyclisation shown here. The Arrhenius parameters for the hydrogen atom transfer to different alkyl radicals could be determined using substituted 5-hexenyl radical clocks. The variations of the activation energies in function of the exothermicity of the reaction and of the polar effects affecting the transition state are discussed.

[1] G. Povie, G. Villa, L. Ford, D. Pozzi, C. H. Schiesser, P. Renaud, *Chem. Commun.* **2010**, 803 – 805.
[2] G. Villa, G. Povie, P. Renaud, *J. Am. Chem. Soc.* **2011**, *133*, 5913 – 5920.

Organic Chemistry, Talk **370**

N-C ylides: stability and reactivity

Tim den Hartog, Juan Manuel Sarria Toro, Joël Gubler, Erik P. A. Couzijn and Peter Chen*

Laboratorium für Organische Chemie, ETH Zürich, Wolfgang-Pauli-Strasse 10, CH-8093 Zürich, Switzerland

Ever since the pioneering work of Nobel laureate George Wittig in the 1960s, ylides have become one of the cornerstones of organic synthesis.[1] However, in contrary to the widely used P-C ylides, N-C ylides are much less frequently used. The lack of widespread application of N-C ylides is presumably due to the general consensus that these reagents are much less stable than their P-counterparts.[2,3]

We are now able to prepare a rather stable (up to 0 °C) N-C ylide in solution. We have studies this N-C ylide extensively by NMR-studies. Furthermore, with the help of both experimental and computational studies we can pinpoint why this N-C ylide is so stable. Finally, we will report on the reactivity of this ylide as alkylidene donor in organic synthesis.[4]

[1] G. Wittig, *Science* **1980**, *210*, 600.
[2] For common rearrangements of N-C ylides, see: a) T. S. Stevens, E. M. Creighton, A. B. Gordon, M. MacNicol, *J. Chem. Soc.* **1928**, 3193; b) M. Sommelet, *C. R. Hebd. Sceances Acad. Sci.* **1937**, *205*, 56.
[3] For theoretical discussion, see: a) J. A. Dobado, H. Martínez-García, J. M. Molina Molina, M. R. Sundburg, *J. Am. Chem. Soc.* **2000**, *122*, 1144; b) I. A. Koppel, R. Schwesinger, T. Breuer, P. Burk, K. Herodes, I. Koppel, I. Leito, M. Mishima, *J. Phys. Chem. A* **2001**, *105*, 9575; c) V. K. Aggarwal, J. N. Harvey, R. Robiette, *Angew. Chem. Int. Ed.* **2005**, *44*, 5468; d) M. J. Calhorda, A. Krapp, G. Frenking, *J. Phys. Chem. A* **2007**, *111*, 2859; e) Y. Fu, H.-J. Wang, S.-S. Chong, Q.-X Guo, L. Liu, *J. Org. Chem.* **2009**, *74*, 810.
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Organic Chemistry, Talk **371**

Stereoselective synthesis of challengingly substituted lactones

Viviana Valerio, Nuno Maulide*

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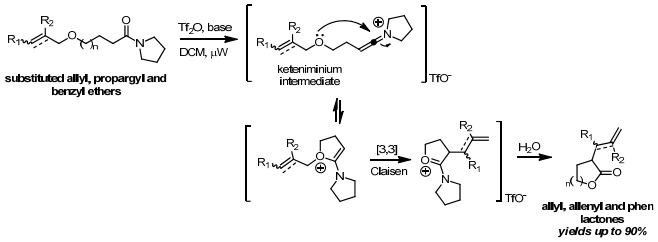
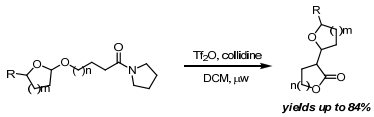
We have discovered an unexpected, selective Claisen-like skeletal reorganisation of δ-alkoxyamides that likely proceeds through the formation of keteniminium intermediates and suggests an exceedingly concise and powerful access to challengingly substituted lactones [1] [2].



We also explored these reactions beyond the field of [3,3] sigmatropic rearrangement chemistry, designing unprecedented O–C shifts [3].



Current efforts are directed to the study of a novel method for the direct lactonisation of protected alcohols onto otherwise inert, stable amides.

[1] C. Madelaine, V. Valerio, N. Maulide, *Angew. Chem. Int. Ed.* **2010**, *49*, 1583.
[2] C. Madelaine, V. Valerio, N. Maulide, *Chem. Asian J.* **2011**, *6*, 2224.
[3] V. Valerio, C. Madelaine, N. Maulide, *Chem. Eur. J.* **2011**, *17*, 4742.

Organic Chemistry, Talk **372**

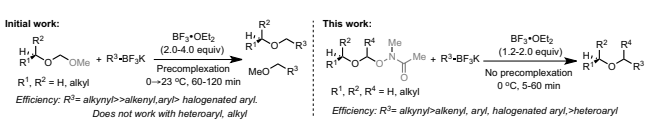
BF_3•OEt_2-Promoted Ether-forming Cross-coupling Reactions of Organotrifluoroborates and Acetals

Cam-Van T. Vo, T. Andrew Mitchell, Jeffrey W. Bode*

Laboratorium für Organische Chemie
Department of Chemistry and Applied Biosciences
ETH–Zürich, Wolfgang Pauli Strasse 10, 8093 Zürich, Switzerland

The ether linkage is fundamental in organic chemistry. Conventionally, it is prepared via Williamson reaction with a basic alkoxide and a halide. Harsh conditions, competitive elimination reactions, however, limit this method in preparing highly substituted ethers and modifying functionalized molecules.

Recently, our group introduced an alternative strategy for the synthesis of dialkyl ethers involving the combination of potassium organotrifluoroborates and *O*-methoxymethyl (*O*-MOM) acetals under mildly acidic conditions.[1] Alkynyl, aryl, vinyl trifluoroborates were suitable substrates; the chemistry could be extended to substituted acetals leading to secondary-secondary ethers. However, as the substrates became more substituted, the regiochemistry eroded. Besides, a relative large excess of organotrifluoroborate and BF_3•OEt_2 along with a precomplexation step were required.



Herein, we report the improved ether-forming cross-coupling reactions of new hydroxamic acid-derived acetals and organotrifluoroborates, as well as the mechanistic studies.[2]

[1] Mitchell, T. A; Bode, J. W. *J. Am. Chem. Soc* . **2009**, *131*, 18057.
[2] Vo, C.-V; Mitchell, T. A; Bode, J. W. *J. Am. Chem. Soc* . **2011**, *133*, 14082

Organic Chemistry, Lecture **373**

Diamide Insecticides: New Sulfonimidoyl and Heterocyclic Anthranilic Derivatives

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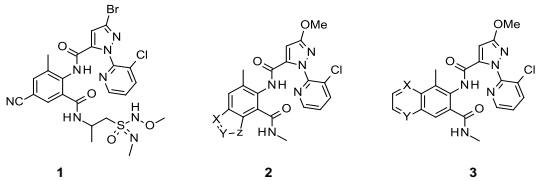
The anthranilic bisamides constitute a new class of crop protection agents, active against phytophagous insects[1]. They are activators of the ryanodine receptors (RyR) which are ubiquitous Ca channels which regulate the Ca release from intracellular stores located in the sarcoplasmic reticulum.

The synthesis of derivatives with novel sulfonimidoyl functional groups[2] and of heterocyclic anthranilic analogues will be presented as well as structure/activity trends. Anthranilamides such as **1** to **3** have *in vitro* activity in the nM range and showed a broad insecticidal spectrum *in vivo*.



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Organic Chemistry, Talk **374**

Peptide Catalyzed 1,4-Addition Reactions of Aldehydes to Nitroolefins – Challenging Nitroolefins and Mechanistic Investigations

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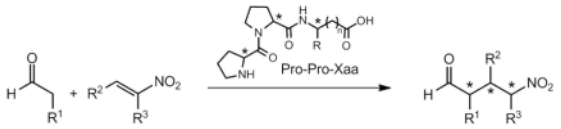
Conjugate addition reactions of aldehydes to nitroolefins are among the most widely researched organocatalytic transformations. One of the most potent catalysts is the tripeptide H-D-Pro-Pro-Glu-NH_2.[1] With its very high activity and selectivity at very low catalyst loadings (0.1 mol%) H-D-Pro-Pro-Glu-NH_2 underlines that short peptides of the type Pro-Pro-Xaa (Xaa = acidic amino acid) are powerful asymmetric catalysts.[1]



The present work is aimed at the extension of the scope of such peptides as catalysts for the 1,4-addition of aldehydes to α,β-disubstituted nitroolefins, a much more challenging and scarcely examined substrate class.[2] Two peptides are presented that allow for reaction of aldehydes with these less reactive nitroolefins. The resulting γ-nitroaldehydes bearing three consecutive stereogenic centers can be further transformed to interesting products such as pyrrolidines or fully substituted γ-butyrolactams and γ-amino acids. Additionally, further investigations reveal mechanistic details that help to rationalize the success of such peptides as organocatalysts.

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Protein Containers Evolved for Encapsulation of Charged Molecules

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D-CHAB ETH Zurich, Wolfgang-Pauli-Strasse 10, Zürich, Switzerland

Numerous proteins in nature form compartments that serve many purposes such as storage and transport of minerals, protein folding, regulation of enzyme catalysis, or nucleic acid delivery. Increasing numbers of natural protein containers (mainly capsid-forming viruses) or their modified versions are being used for nanotechnology, with detailed applications ranging from controlled synthesis of novel materials, catalysis and bioimaging to drug delivery and gene therapy. Research on basic mechanisms of encapsulation processes is also important to understand compartmentalization inside living organisms. In our lab, we have shown the possibility of engineering a capsid protein (*Aquifex aeolicus* lumazine synthase AaLS) to encapsulate charged guest molecules by introducing oppositely charged residues which drive selective electrostatic binding of the guests in vivo. We also demonstrated that it is possible to optimize the loading of such capsids towards a defined charged guest. A toxic enzyme (charged HIV protease) was produced at high intracellular concentrations, as its immediate encapsulation reduced the toxicity and allowed for cell survival. Here, we report selective loading of an engineered AaLS capsid in vitro with large amounts of desired cargo resulting in a stable complex, where formation is driven by simple electrostatic host-guest interactions. Two types of modified AaLS capsids were produced and used for encapsulation. One with a negatively charged interior to trap positive cargo, and the other with a positively charged internal surface to attract negatively charged molecules. The former was used to capture positively charged GFP; the latter encapsulates negatively charged GFP as well as oligonucleotides and gold nanoparticles.

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Organic Chemistry, Talk **376**

MR-active LDL nanoparticles for *in vivo* imaging of atheroplaques

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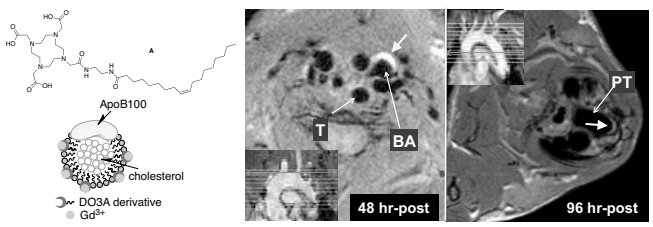
Cardiovascular disease remains the leading cause of death in the western world and early detection of vulnerable atheroplaque is highly demanded. In this study, we aim to detect atheroplaques using LDL as a selective delivery vehicle. A new DO3A-monoamide derivative with a long alkenyl anchor (**A**) was synthesized and used for the intercalation into the lipid monolayer of LDL. Subsequent chelating reaction with Gd^{3+} citrate and removal of excess Gd^{3+} by tropolone provided Gd^{3+}-functionalized LDL (Gd^{3+}-LDL) with a high payload (>200 Gd^{3+} per particle). The DLS and CryoTEM analyses indicated that the Gd^{3+}-LDL had similar particle size as LDL without aggregation. *In vivo* tests using model mice (*ApoE*$^{-/-}$ and *LDLr*$^{-/-}$ fed with high fat diet) showed that Gd^{3+} was selectively accumulated into the plaques of model mice as analyzed by ICP-MS of tissues from model mice and normal wild type controls. *In vivo* MR imaging of *ApoE*$^{-/-}$ showed high enhancement in brachiocephalic artery (BA) and pulmonary trunk (PT).



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Organic Chemistry, Talk **377**

Copper catalyzed asymmetric conjugate addition of alkenylalanes to 2,3-dehydro-4-piperidones

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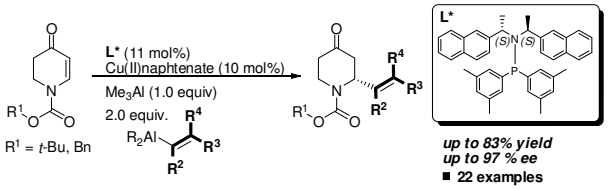
Recently, we disclosed two methodologies for the creation of quaternary stereogenic centers by addition of alkenyl alanes to β-substituted cyclic enones.[1] Next, we were interested in other challenging substrates which might be more useful for synthetic applications. 2,3-dehydro-4-piperidones, potential precursors for piperidine alkoloids, appeared to be particularly interesting as no addition of alkenyl nucleophiles to this substrate class is known, and several research groups were not able to introduce such groups. Therefore, we tested our methodologies for this class of substrates and were pleased to see that the corresponding adducts were formed in high enantioselectivities and good yields.[2]



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Organic Chemistry, Talk **378**

Total Synthesis of the Bacterial RNA Polymerase Inhibitor Ripostatin B

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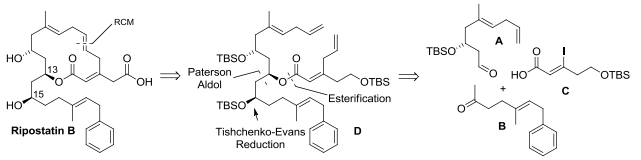
Due to the increasing number of bacterial pathogens resistant to antibiotic treatment, the search for new antibiotics with a different mode of action is crucial. Ripostatin B is a 14-membered macrolide of myxobacterial origin, first isolated in 1995.[1] The compound shows a narrow spectrum of antibiotic activity and presumably inhibits bacterial RNA polymerase by a different mode of action than the well-established anti-tuberculosis drug rifampicin.

In order to provide a basis for SAR studies on ripostatin, we have developed an efficient modular total synthesis of ripostatin B, based on building blocks **A**, **B**, and **C**.[2] The longest linear sequence comprises 21 steps and furnished the target molecule in 3.6% overall yield. Key steps are a ring closing olefin metathesis with ester **D**, an esterification reaction (to produce **D**), a Paterson aldol reaction (to set the stereocenter at C13), and a Tishchenko-Evans reduction (to establish the stereocenter at C15); the latter transformations proceeded with exquisite stereoselectivity.



This contribution will discuss the details of the syntheses of building blocks **A**, **B**, and **C** and their assembly into ripostatin B.

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Organic Chemistry, Talk **379**

Supramolecular Approaches to Intercalate Hydrogen-Bonded Surface Networks

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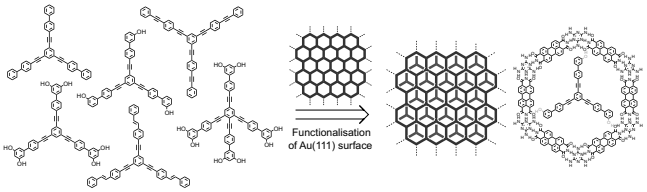
Functionalised surfaces require precise control of substituent architecture and surface morphology. Bottom-up approaches to achieve this surface functionalisation have been achieved by intercalating a melamine based hydrogen-bonded porous network from solution.[1] Expanding on this work we have used this porous network as a template to host single-molecule rods.



The synthesis of the stars was non-trivial and facilitated by extending an acetylene scaffold with a modular convergent approach.[2] Here we report the synthesis, crystal structure determination and STM investigations of a family of star shaped-molecular rods demonstrating single molecule organisation in an extended array.

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Towards Heterometallic Molecular Grids: Synthesis of Bipyridine and Terpyridine-Based Polytopic Ligands

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[2]Chaoyang University of Technology/ Department of Applied Chemistry, 168, Jifeng E. Rd., Wufeng District, Taichung, 41349 Taiwan, R.O.C.

Tridentate 2,2′:6′,2″-terpyridine and bidentate 2,2′-bipyridine have attracted the attention of researchers because of their ability to form complexes of different geometries with a variety of metals [1]. Incorporation of these two structural motifs into one ligand, as well as directing both terpyridine and bypiridine units into a linear topology (Figure 1) open new perspectives in the construction of heterometallic molecular grids [2].

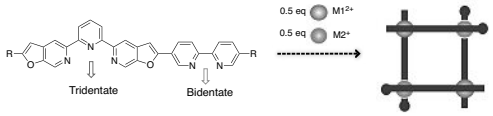

Figure 1. Mixed tridentate 2,2′:6′,2″-terpyridine and bidentate 2,2′-bipyridine based ligands.

In our pursuit to construct heterometallic molecular grids, we have developed a robust synthesis of 2,6-bis(2-substituted-furo[2,3-c]pyridine-5-yl)pyridine based ligands where the fused furan rings act as directing groups placing substituents in an orthogonal topology. The synthesis of various metal complexes of these novel ligands reveals their feasibility as promising building blocks in supramolecular chemistry.

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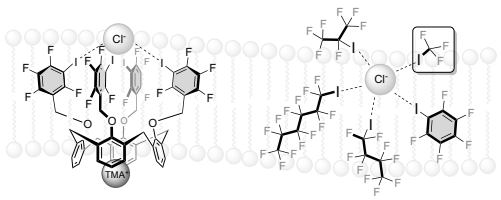
Organic Chemistry, Talk **381**

Anion-π Interactions and Halogen Bond in Action

Andreas Vargas Jentzsch, Daniel Emery, Jiri Mareda, Naomi Sakai, Stefan Matile*

Department of Organic Chemistry, University of Geneva, Geneva, Switzerland

The creation of supramolecular functional systems is undoubly of paramount importance. In this context, the available interactions should be widened as much as possible. Whereas anion-π interactions were only recently caught at work, here we extend this concept with insights on the processes underneath [1].



In this report we mainly focus on halogen bonds, which are explored in a systematic manner going from a big preorganized covalent systems [2] to the unexpected highlight of a single carbon halogen-bond donor capable to self-assemble in the lipid bilayer membrane and form a supramolecular anion transport system.

The power of supramolecular chemistry is underlined by this combination of non-covalent self-assembly, intrinsic variations of the properties but, more importantly, function.

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Indoline Synthesis via Catalytic Asymmetric Coupling of an Unactivated Methylene Group

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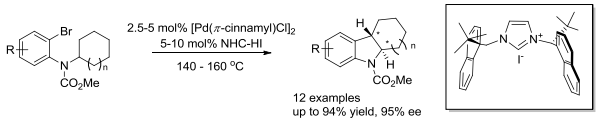
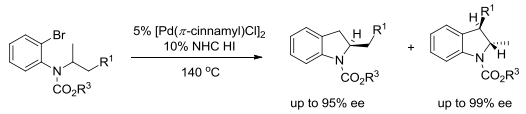
Herein we describe an extraordinarily efficient palladium-NHC catalyzed synthesis of highly enantioenriched 2,3-*trans*-fused indolines via asymmetric C(sp^3)-H activation of an unactivated methylene unit. [1] It is noteworthy that this C-C coupling delivers the products with enantioselectivities of up to 95% ee despite the high temperature (140 – 160 °C) required. Key in this reaction was the use of new bulky chiral carbene ligands and the high thermal stability of their Pd-complexes.



The initial results were extended to the synthesis of 2-substituted and 2,3-disubstituted indolines. Racemic substrates reacted via highly asymmetric regiodivergent reactions. [2]



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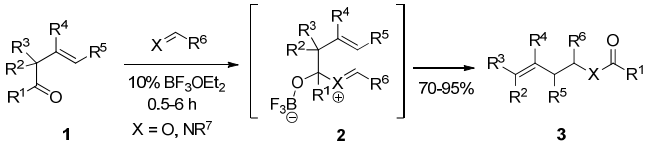
Novel Intermolecular Azonia- and Oxonia-Cope Rearrangements

A. Goeke,[1] Y.Zou,[2] L. Zhou,[2] J. Ding,[2] P. Kraft,[1] F. Schoenebeck[3]

[1]Givaudan Schweiz AG, Űberlandstr.138, CH-8600 Dübendorf, [2]Givaudan Fragrances (Shanghai) Ltd,298 Li Shi Zhen Road, Shanghai, 201203, P.R. China, Laboratorium für Organische Chemie, [3]ETH Zürich, Wolfgang-Pauli-Str.10, CH-8093 Zürich

A conceptually novel cross-dimerization of β,γ-unsaturated carbonyl compounds[1] with another aldehyde gives access to homoallylic esters and lactones. The transformation is Lewis acid catalyzed and proceeds atom-economically via disproportionation of the carbonyl groups through organized oxonia-Cope transition states. A stereoselective [n+4] ring enlargement leading to a variety of 9-16 membered macrolides is described.[2,3] The approach can be further extended to imines as reaction partners, giving rise to homoallylic amides and lactams. The scope of this preparatively useful reaction as well as its stereochemical and mechanistic implications will be discussed.



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Organic Chemistry, Talk **384**

Etheno-adenine generation at specific sites

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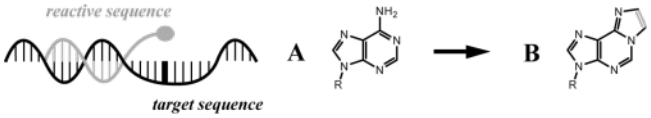
The so-called etheno-bases (ε-bases) are known to be involved in carcinogenesis. On the one hand they are found in genomes of organisms that have been exposed to carcinogens such as vinyl chloride and on the other hand they are formed endogenously in various organisms, including humans [1]. Another well-known feature especially of ε-adenine (**B**) is its strong fluorescence that has been exploited for different applications [2, 3].



The state of the art to form short oligodeoxynucleotides containing ε-adenine in specific positions is solid phase synthesis [4]. In this study, however, we report the successful development of a new method starting from an unmodified *target sequence* and thus allowing the facile site-specific generation of ε-adenine also in longer strands. The site-specific conversion of adenine (**A**) to its corresponding ε-base is induced by a so-called *reactive sequence* carrying a chemically reactive group which is guided to the modification site by the intrinsic base pairing properties of nucleic acids.

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Financial support from the Swiss National Science Foundation is gratefully acknowledged (SNSF-Professorship PP002-119106/1 to EF).

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Enol-Acetal Synthesis Via Carbenoid C-H Insertions Into Tetrahydrofurans Catalyzed By CpRu Complexes

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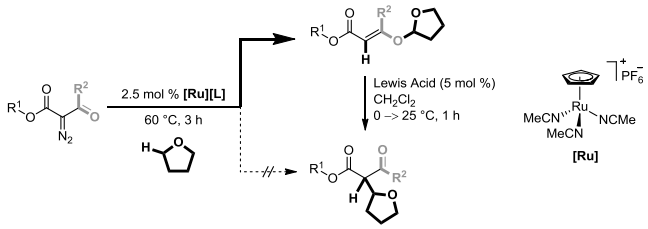
CpRu complexes are known to catalyse together the decomposition of α-diazo derivatives [1]. Recently our group has shown that combinations of [$CpRu(CH_3CN)_3$][PF_6] and diimine ligands lead to O-H insertion and condensation reactions with nitriles, ketones and aldehydes [2]. In a new development that use α-diazo-β-ketoesters and THF moieties as substrates, we report the kinetically favored formation of C-O instead of C-C bond adducts [3]. The mild reaction conditions yield novel enol-acetal motifs through unprecedented 1,3-C-H insertion reactions. A Lewis acid catalysed rearrangement to the classical C-C bound adducts is possible.



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Organic Chemistry, Talk **386**

A Concise Total Synthesis of (±)-Trigonoliimine B

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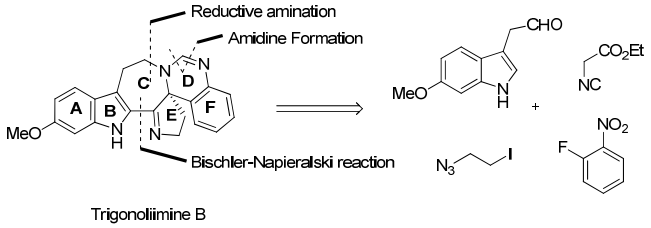
Trigonoliimine **B** belongs to the family of oxidatively rearranged bisindole alkaloids. It was isolated, along with trigonoliimines **A** and **C**, by Hao and coworkers in 2010 from the leaves of *Trigonostemon lii* Y. T. Chang collected in Yunnan Province of China.[1] Structurally, trigonoliimine **A** and **B** contain a quaternary carbon whose four substituents are cross-linked to form the 5-, 6- and 7-membered tricyclic core of the hexacyclic structure.

We present our efforts that culminated in total synthesis of trigonoliimine **B** in 7 steps from commercially available starting materials with an overall yield of 12%.[2] The synthesis features the use of an α-isocyanoacetate as a glycine template for the preparation of an α,α-disubstituted α-amino ester that is appropriately functionalized for the construction of C, D and E rings. Sulfolane was found to be the solvent of choice for an unprecedented Bischler-Napieralski reaction implemented for the construction of a seven-membered ring with concurrent formation of an *exo*-imine function.



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Organic Chemistry, Talk **387**

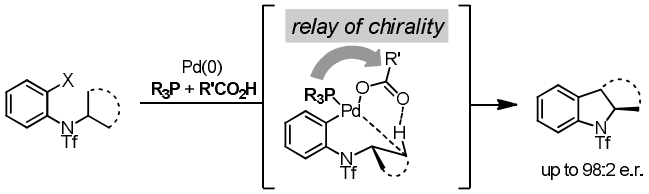
Chiral Monodentate Phosphines and Carboxylic Acids:

Cooperative Effects in Palladium-Catalyzed Enantioselective C(sp^3)-H Functionalization

Tanguy Saget[1,2], Nicolai Cramer[1]

[1]Laboratory of Asymmetric Catalysis and Synthesis, EPF Lausanne. EPFL SB ISIC LCSA, CH-1015 Lausanne, Switzerland
[2]Laboratory of Organic Chmistry, ETH Zurich. Wolfang-Pauli-Strasse 10, CH-8093 Zurich, Switzerland

The enantioselective functionalization of C(sp^3) H bonds is a challenging task in asymmetric catalysis. Over the last decade, elucidation of the concerted metalation-deprotonation (CMD) mechanism for the palladium-catalyzed C(sp^3) H activation has largely contributed to the progress in this area.[1] However, the harsh reaction conditions required for such transformations and the lack of suitable ligands hampered the development of asymmetric versions. Herein, we report the enantioselective intramolecular arylation of unactivated methyl and methylene C(sp^3) H bonds in excellent selectivities.[2] The key of our strategy is based on the design of new electron-rich monodentate phosphines working in cooperation with a bulky carboxylate which acts as a relay of chirality during the enantiodiscriminating CMD step.



[1] S. Rousseaux, S. I. Gorelsky, B. K. W. Chung, *J. Am. Chem. Soc.* **2010**, *132*, 10692.

[2] T. Saget, S. J. Lemouzy, N. Cramer, *Angew. Chem. Int. Ed.* **2012**, *51*, 2238.

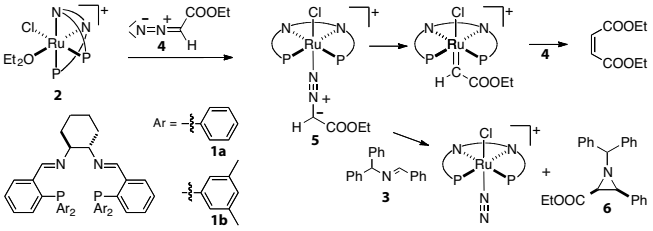
Organic Chemistry, Talk **388**

Asymmetric Imine Aziridination with Ru/PNNP: Ligand Tuning

A. Schira, J. Egloff, A. Mezzetti*

ETH Zürich, D-CHAB, Wolfgang-Pauli-Str. 10, 8093 Zürich

We recently reported[1] the use of [RuCl(OEt$_2$)(**1a**)]PF$_6$ (**2a**PF$_6$) catalyzes the asymmetric aziridination of imine **3** with ethyl diazoacetate **4** under a strict gradient temperature protocol. NMR spectroscopic studies showed that **4** coordinates to give the diazoester complex **5**, which either transfers carbene to the imine to give aziridine **6** or decomposes to a carbene complex that is responsible for the formation of diethyl maleate and, thus, for the low yield.



Since bulky ligands are known to inhibit carbene formation from diazoester complexes,[2] we prepared a series of substituted PNNP ligands and used them in the catalytic aziridination of **3**. With ligand **1b** in particular, [RuCl(OEt$_2$)(**1b**)]BF$_4$ (10 mol%) gave aziridine **6** in 25% yield and 93% ee at 0 °C. Using an excess of **4** (4 equiv) increased the yield of **6** to 39% with the same enantioselectivity, which is significantly improved with respect to **2a**PF$_6$ (26% yield, 84% ee). The use of BF_4^- as counterion is pivotal, as PF_6^- is hydrolyzed upon activation of [RuCl$_2$(**1b**)] with (Et$_3$O)PF$_6$, and the resulting acid catalyzes a nonenantioselective aza-Darzens background reaction between **3** and **4**. The results with other bulky ligands will be presented.

[1] M. Ranocchiari, A. Mezzetti, *Organometallics* **2009**, *28*, 3611.

[2] J. Zhang, M. Gandelman, L. J. W. Shimon, D. Milstein, *Organometallics* **2008**, *27*, 3526.

Organic Chemistry **389**

Redox-Switchable Resorcin[4]arene Cavitands

Igor Pochorovski[1], Corinne Boudon[2], Jean-Paul Gisselbrecht, Marc-Olivier Ebert[1], W. Bernd Schweizer[1], François Diederich[1*]

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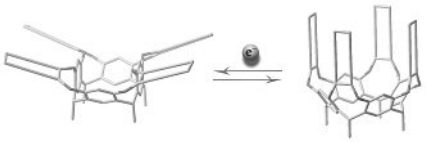
Quinoxaline-bridged resorcin[4]arene cavitands have the ability to undergo a triggered conformational transition from a contracted, vase state, to an open, kite state.[1] This precisely defined conformational change makes them ideal for use as switches, receptors, or molecular grippers. However, to parlay the dynamic behavior of the cavitands into such advanced materials, it is important to create cavitands with more practical switching modes.[2]



Towards this goal, we developed quinone-based redox-switchable cavitands which can be applied in the area of nanorobotics, as molecular grippers.

[1] V. A. Azov, A. Beeby, M. Cacciarini, A. G. Cheetham, F. Diederich, M. Frei, J. K. Gimzewski, V. Gramlich, B. Hecht, B. Jaun, T. Latychevskaia, A. Lieb, Y. Lill, F. Marotti, A. Schlegel, R. R. Schlittler, P. J. Skinner, P. Seiler, Y. Yamakoshi, *Adv. Funct. Mater.* **2006**, *16*, 147 – 156.

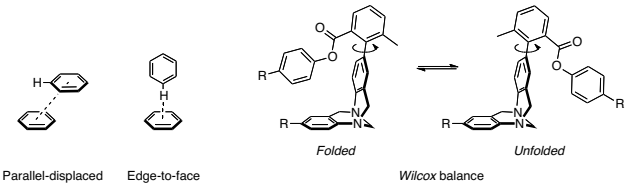
[2] I. Pochorovski, C. Boudon, J.-P. Gisselbrecht, M.-O. Ebert, W. B. Schweizer, F. Diederich, *Angew. Chem. Int. Ed.* **2012**, *51*, 262-266.

Organic Chemistry **390**

Substituent effects on the edge-to-face CH/π interaction

Haraldur Gardarsson[1], W. Bernd Schweizer[1], François Diederich[1]

[1] ETH Zürich, Wolfgang-Pauli-Strasse 10, 8093 Zürich, Switzerland



Noncovalent interactions involving aromatic rings are pervasive throughout chemical and biological recognition.[1] Of the arene–arene interactions, two geometries are favoured, the parallel-displaced and the edge-to-face interactions. The quantification of the latter being the focus of this research. In particular the effect of substituents on the interaction will be investigated, as it is a topic under debate, both in theoretical and experimental studies.[2-5]

To examine these interactions we have utilized the *Wilcox* balance.[5] This unimolecular torsion balance places two aromatic rings in the correct geometry for an edge-to-face interaction. The thermodynamic equilibrium between the folded and unfolded atropisomers can be determined by ^{1}H NMR and utilized to calculate the folding free enthalpy.

[1] L. M. Salonen, M. Ellermann, F. Diederich, *Ang. Chem. Int. Ed.*, **2011**, *50*, 4808.
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Organic Chemistry **391**

Host–Guest Complexation with Resorcin[4]arene-Based Container Molecules

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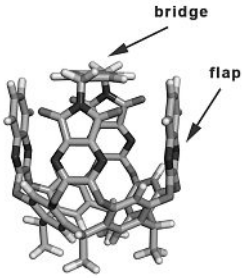
[1]ETH Zürich, Laboratorium für Organische Chemie, Wolfgang-Pauli-Strasse 10, CH-8093 Zürich (Switzerland)
[2]Oklahoma State University, Department of Chemistry, 107 Physical Science, Stillwater, OK 74074 (USA)



Host–guest complexation studies were performed with a resorcin[4]arene-based container molecule as host and a variety of cycloalkanes and alicyclic heterocycles as guests. Association constants were determined by ^{1}H NMR and isothermal titration calorimetry (ITC). The reversible conformational switching of the host (containing a rigidifying bridge and two switchable flaps) was investigated by ^{1}H NMR spectroscopy. Non-covalent interactions between host and guest were further studied using thermodynamic data from ITC.

[1] J. Hornung, D. Fankhauser, L. D. Shirtcliff, A. Praetorius, W. B. Schweizer, F. Diederich, *Chem. Eur. J.* **2011**, *17*, 12362.

Organic Chemistry **392**

Synthesis and structure determination of bicyclic bridged peptides

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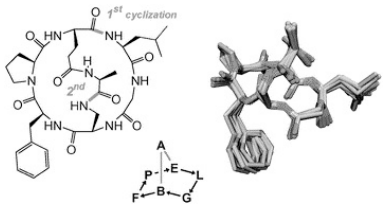
The use of branching amino acids in a peptide sequence, like diamino acids (as used in peptide dendrimers[1]) or amino diacids, allows to design bicyclic homodetic peptides such as the "norbornapeptides" (bicyclo[2.2.1]heptapeptides), which were prepared using an orthogonal protection scheme. The first cyclization is performed on resin after selective deprotection of a glutamic acid residue, whereas the second ring closure is achieved by amide bond formation at high dilutions.



These peptides are structurally well-defined and cover an almost pristine area of peptide topological space.[2] Their conformational rigidity was investigated by means of 2D-NMR and X-ray crystallography and may offer a platform to design drugs tackling protein-protein interactions.

[1] T. Darbre, J.-L. Reymond, *Org. Biomol. Chem.* **2012**, *10*, 1483.
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Organic Chemistry **393**

ACCESS Swiss Chemical Library: Design of a Diverse Screening Collection for Chemical Biology using Molecular Shape

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[1]Biomolecular Screening Facility, NCCR Chemical Biology EPFL, CH-1015, Lausanne, Switzerland

One of the important tasks within the NCCR Chemical Biology is the creation of the ACCESS high-throughput screening platform. Key aspect during the creation is the purchase of a chemically diverse collection of small molecules that will be available to our research community during screening campaigns. Although the importance of shape during the drug discovery has been reported, only a small number of applications have been used to understand the importance of the shape diversity within a screening collection in order to address a wide variety of biological targets seen in a screening platform.[2,3]
In particular for primary screening it is highly desirable that multiple distinct series of chemical compounds get identified to anticipate downstream issues that may arise for a given chemical family.[2] Whereas these descriptors have been merely used for analytical purposes of existing screening collections, we herein present our approach for the creation of a 50k large diverse screening collection, in which the use of descriptors of molecular shape has been privileged.

[1] Nicholls A *et al.*, *J. Med. Chem.* **2010**, *53*, 3862-86.
[2] Sauer WHB, Schwarz MK, *Chimia* **2003**, *57*, 276-83.
[3] Lovering F, Bikker J, Humblet C, *J. Med. Chem.* **2009**, *52*, 6752-56.

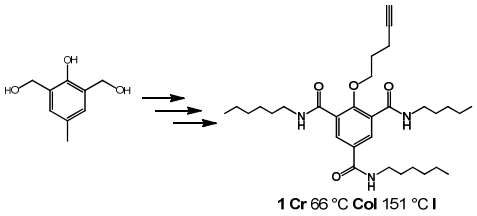
Organic Chemistry **394**

New dimers of benzene triamide for high organization in liquid crystal mesophases

Christian Invernizzi, Reinhard Neier*

Institute of Chemistry, University of Neuchâtel,
Av. De Bellevaux 51, case postale 158, 2009, Neuchâtel, Switzerland

Discotic Liquid Crystals (DLc's) are well known in the field of organic materials[1], due to their interesting properties like 1D charge transport[2,3]. Reducing the degree of freedom by making dimers has been shown to increase the conductivity[4]. Our aim is to use an aromatic linker as a probe to study the intermolecular self-assembly. The synthesis of the discogenic monomeric precursor **1** was completed, showing mesomorphic proprieties.



Our attention is now focused on the design and screening of different types of aromatic linkers, in order to provide a rational understanding of the self-assembly in a discotic liquid crystal systems.

[1] Müllen. K., *Science*, **2001**, *293*, 1119
[2] Destrade, C.; Mondom, M.C.; Malthete, J.;*J. de Physique*, **1979**, *C3* ; 17
[3] Laschat, S., et al., *Angew. Chem. Int. Ed.* **2007**, *46*, 4832
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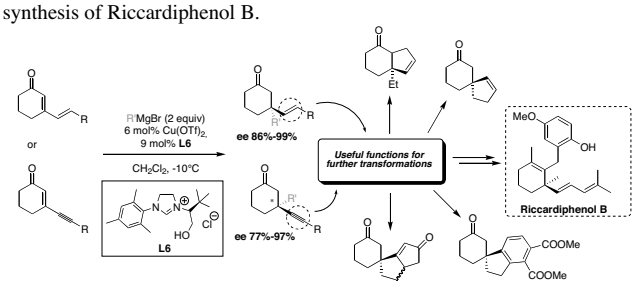
Organic Chemistry **395**

Formation of quaternary stereogenic centers by NHC-Cu catalysed asymmetric conjugate addition reactions with Grignard reagents on polyconjugated cyclic enones toward the total synthesis of Riccardiphenol B.

Matthieu Tissot, Christian Bleschke, Marc Mauduit*, Alexandre Alexakis*

University of Geneva, 30, quai Ernest Ansermet, 1211 Genève, Switzerland

The copper catalyzed conjugate addition of various Grignard reagents to polyconjugated enones (dienones and enynones derivatives) are reported. The catalyst system, composed of copper triflate and the NHC ligand **L6**, led to the unsual selective formation of the 1,4 addition products. The reaction allows the creation of all-carbon chiral quaternary centers with enantiomeric excess up to 99%. The remaining insaturation on the 1,4 adducts gave an access to valuable synthetic transformations especially to the total synthesis of Riccardiphenol B.



[1] Henon, H.; Mauduit, M.; Alexakis, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 9122.
[2] Tissot, M.; Pérez Hernandez, A.; Müller, D.; Mauduit, M.; Alexakis, A. *Org. Lett.* **2011**, *13*, 1524.
[3] Tissot, M.; Pogialli, D.; Müller, D.; Mauduit, M.; Alexakis, *Chem. Eur. J.* **2012** *in press*.

Organic Chemistry **396**

Asymmetric conjugate addition to polyconjugated Michael acceptors – Application towards the total synthesis of Riccardiphenol B

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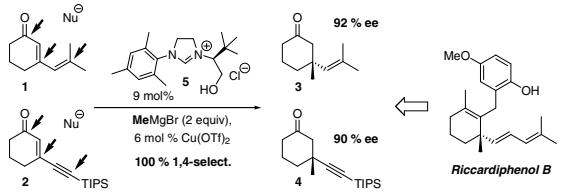
[1]Université de Genève, Departement de Chimie Organique, Quai Ernest Ansermet 30, 1211 Genève, Schwitzerland

Asymmetric conjugate addition (ACA) is a powerful tool to install quaternary stereogenic centers in five or six membered rings with high enantiomeric excess.[1] Alexakis and coworkers recently achieved high 1,4-selectivity and excellent enantioselectivities with polyconjugated substrates by using the privileged N-heterocyclic carbene **5** as ligand.[2] The remaining vinyl or acetylene substituents constitute very versatile functional groups which shall be demonstrated by the total synthesis of *Riccardiphenol B*.



Since the conjugate addition forms the corresponding enolate, the reaction can also be used to selectively install the adjacent substituent in the α-Position and represents therefore clearly the key step of the envisaged total synthesis.[3]

[1] T. Jerphagnon, M. G. Pizzuti, A. J. Minnaard, B. L. Feringa, *Chem. Soc. Rev.* **2009**, *38*, 1039.
[2] H. Hénon, M. Mauduit, A. Alexakis, *Angew. Chem. Int. Ed.* **2008**, *47*, 9122.
[3] T. L. May, J. A. Dabrowski, A. H. Hoveyda, *J. Am. Chem. Soc.* **2011**, *133*, 736.

Organic Chemistry **397**

Copper free asymmetric allylic alkylation using Grignard reagents on bifunctional allylic bromides.

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University of Geneva
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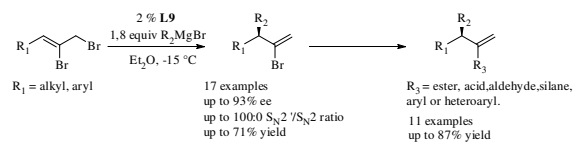
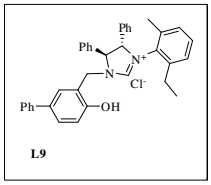
A series of substrates, containing a vinylic bromide were employed in copper-free methodology using bidendate NHC ligands. The desired compounds are generally obtained with good enantioselectivity and good regioselectivity. Importantly the copper catalyzed system afforded lower enantioselectivity value. The catalytic products could be transformed into a broad scope of new 1, 1-disubstituted olefins in a single step transformation without erosion of the enantioselectivity.





[1] D. Grassi, A. Alexakis, *Org.Lett*. **2012**, 14,1568-1571.

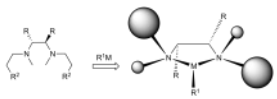
Organic Chemistry **398**

Evaluation of the Chiral DIANANE Backbone as Ligand for Organolithium Reagents

Praz Jézabel [1], Laure Guénée[1], Sarwar Aziz [2], Albrecht Berkessel*[2], and Alexandre Alexakis*[1]

[1] University of Geneva, 30 Quai Ernest-Ansermet, CH-1211 Geneva, Switzerland
[2] University of Köln, 4 Greinstrasse, D-50939 Köln, Germany

Chiral 1,2 diamines are compounds of great interest in organic synthesis, particularly as chiral ligands for various asymmetric reactions. Previously in our laboratory, we observed a chirality transfer to the nitrogen atoms which become stereogenic upon chelation with a metal.



The accuracy of this concept was then illustrated in various reactions such as asymmetric bromine-lithium exchange, enantioselective additions of aryl and alkyllithium reagents to aromatic imines [1]. Toward this end, we developed a new type of C_2-symmetric tertiary diamines derived from the DIANANE backbone. These new chiral ligands owe a rigid backbone and larger fixed distance between the two nitrogen atoms. They have been involved in diverse asymmetric synthesis using organolithium reagents and compared with the previous 1,2 chiral diamine ligands [2].

[1] Q. Perron, A. Alexakis, *Adv. Synth. Catal.* **2010**, *352*, 2611-2620
[2] Praz Jezabel, Laure Guénée, Sarwar Aziz, Albrecht Berkessel and Alexandre Alexakis , *Adv. Synth. Catal.* **2012**, *Accepted manuscipt*.

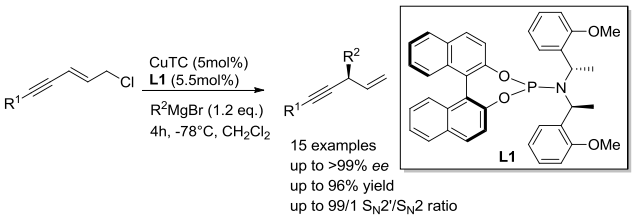
Organic Chemistry **399**

Copper-Catalyzed Asymmetric Allylic Alkylation of Extended Multiple Bond Systems

Hailing Li[1], Alexandre Alexakis[1]

[1]University of Geneva, 30 Quai Ernest Ansermet, 1211 Geneva, Switzerland

Copper-catalyzed asymmetric allylic alkylation (AAA) is one of the most useful and efficient carbon-carbon bond formation methods, leading to optically enriched molecules.[1] Our group has reported highly regio- and enantioselective copper-phosphoramidite catalytic system for asymmetric allylic alkylation (AAA) on allylic chlorides employing organomagnesium reagents.[2]
Herein, a series of prochiral enyne chlorides was reported as substrate in the copper-catalyzed AAA, using Grignard reagents as nucleophile. Excellent 1,3-substitution regioselectivities and good to excellent enantioselectivities were achieved.[3]



Substrate diversity is further extended to diene chlorides.

[1] For a recent review, see: A. Alexakis, J. E. Bäckvall, N. Krause, O. Pamies, M. Dieguez, *Chem. Rev.* **2008**, *108*, 2796.
[2] K. Tissot-Croset, D. Polet, A. Alexakis, *Angew. Chem. Int. Ed.* **2004**, *43*, 2426.
[3] H. Li, A. Alexakis, *Angew. Chem. Int. Ed.* **2012**, *51*, 1055.

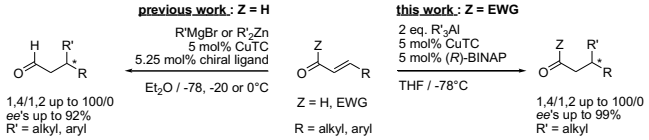
Organic Chemistry **400**

Enantioselective Copper Catalyzed 1,4-addition to challenging 1,2-Dicarbonyl like Michael acceptors

Sylvie Goncalves, Ludovic Gremaud, Alexandre Alexakis*

University of Geneva, Faculty of Sciences, Quai Ernest-Ansermet 30
Department of organic chemistry, CH-1211 Geneva 4, Switzerland

The copper-catalyzed asymmetric conjugate addition (ACA) of organometallic reagents to Michael acceptors is among the most important methodologies to form a C-C bond in an enantioselective manner. In this field, a variety of α,β-unsaturated compounds have been successfully used.[1] However, α,β-unsaturated aldehydes are more challenging substrates because of their high reactivity toward the undesired 1,2-addition and aldol by-products.[2] More recently, β,γ-unsaturated 1,2-dicarbonyl compounds emerged to be a new class of challenging Michael acceptors for this key transformation.[3] Scope and limitations of the ACA to such substrates will be presented as well as their potential synthetic applications.



[1] (a) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221; (b) Alexakis, A.; Backväll, J. E.; Krause, N.; Pamies, O.; Dieguez, M. *Chem. Rev.* **2008**, *108*, 2796; (c) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824.
[2] Palais, L.; Babel, L.; Quintard, A.; Belot, S.; Alexakis, A. *Org. Lett.* **2010**, *12*, 1988.
[3] Gremaud, L.; Alexakis, A. *Angew. Chem. Int. Ed.* **2012**, *51*, 794.

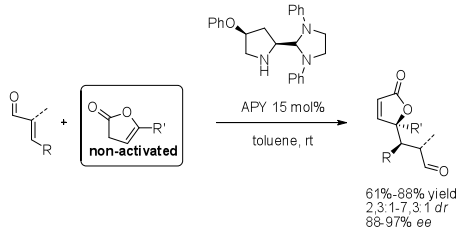
Organic Chemistry **401**

Highly Enantioselective Direct Vinylogous Michael Addition of γ-Butenolide to Enals

Alice Lefranc, Adrien Quintard, Alexandre Alexakis*.

University of Geneva, Quai Ernest Ansermet 30, 1211 Geneva 4, Switzerland.

In recent years, aminocatalysis and particularly iminium catalysis has become an essential activation mode for the asymmetric β-functionalization of conjugated carbonyl compounds. Our group recently developed Aminal-PYrrolidine (APY) catalysts as powerful tools for aminocatalyzed reactions.[1] In this context, we disclosed the development of an unprecedented and simple direct vinylogous addition of deconjugated butenolide to enals in excellent stereoselectivities (>95% *ee*).[2] This methodology allows for the efficient preparation of complex γ-butenolide from Angelica lactone derivatives, directly obtained from readily available renewable resources. Furthermore, preliminary mechanistic investigations allowed for a better understanding of the process.



[1] a) A. Quintard, C. Bournaud, A. Alexakis, *Chem. Eur. J.*, **2008**, *14*, 7504-7507 ; b) A. Quintard, S. Belot, E. Marchal A. Alexakis, *Eur. J. Org. Chem.*, **2010**, 927-936.
[2] A. Quintard, A. Lefranc, A. Alexakis, *Org. Lett.*, **2011**, *13*, 1540-1543.

Organic Chemistry **402**

Copper-Catalyzed Asymmetric Conjugate Addition of Organoaluminium Reagents to α,β-Unsaturated Lactams

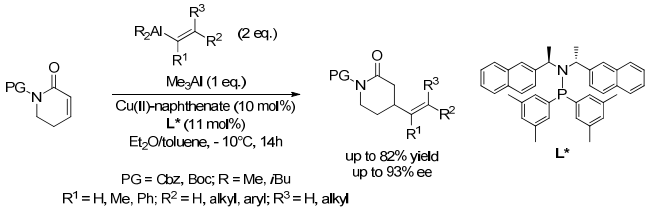
Pierre Cottet, Alexandre Alexakis*

University of Geneva, Quai Ernest Ansermet, 30
CH-1211 Geneva, Switzerland

Since nitrogen heterocycles are ubiquitous in compounds of pharmaceutical interest, much effort has been dedicated to the development of asymmetric methodologies to access chiral nitrogen containing compounds.

Among the main reactions in organic synthesis, the asymmetric conjugate addition (A.C.A.) is a powerful tool for enantioselective C-C bond formation. A.C.A. of various alkyl and aryl nucleophiles to α,β-unsaturated lactams has been reported. However, the addition of alkenyl substituents in β-position remains challenging, and would lead to interesting building blocks.

We recently reported the copper-catalyzed asymmetric Michael addition of alkenyl alanes to *N*-substituted-2,3-dehydro-4-piperidones [1]. The optimized conditions were then applied to six-membered α,β-unsaturated lactams, affording easily functionalizable products. Moderate to good yields (up to 82%) and high levels of enantioselectivity (up to 93%) were achieved, by using a combination of copper(II)-naphthenate and a phosphinamine ligand.



[1] D. Müller, A. Alexakis, *Org. Lett.* **2012**, *14*, 1842.

Organic Chemistry **403**

Asymmetric bromine-lithium exchange: development of new chiral diamines and applications in catalysis

Julien Graff and Alexandre Alexakis[1]

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Halogen-lithium exchange is a powerful tool in organic synthesis. The treatment of an aryl halide with an alkyllithium reagent, like *n*-BuLi, promotes the formation of the corresponding lithiated compound. This aryllithium species can be further functionalized to access to molecules of higher complexity.

Diamines, like TMEDA, are known to be usefull accelerators of this reaction by breaking up the corresponding lithium-aggregates. Therefore, we successfully employed chiral diamines for the asymmetric bromine-lithium exchange of polybrominated aromatic prochiral compounds leading to axially chiral molecules in good yields (up to 89 %) and enantiomeric excesses (up to 72 %). Finally, it is important to mention that a double bromine-lithium change has to be performed to induce asymmetry in the final molecule.

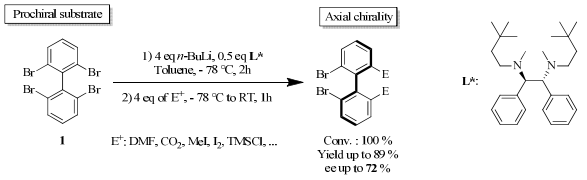


Fig. 1: Asymmetric bromine-lithium exchange on 2,2',6,6'-tetrabromobiphenyl **1**.

[1] Perron Q., Alexakis A., *Adv. Synth. & Catal.,* **2010**, *352*, 2611.

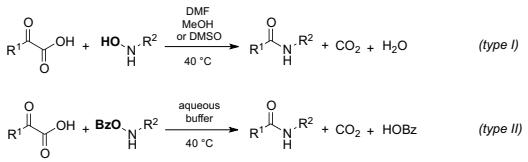
Organic Chemistry **404**

The Mechanism of the α-Ketoacid-Hydroxylamine (KAHA) Amide-Forming Ligation

Ivano Pusterla, Jeffrey W. Bode

ETH Zürich, Wolfgang-Pauli-Strasse 10, 8093 Zürich, Switzerland

The α-ketoacid-hydroxylamine (KAHA) ligation reaction allows the chemoselective formation of amide bonds under very mild conditions and produces only water and carbon dioxide (*type I*) or benzoic acid (*type II*) as byproducts [1].



We have already demonstrated that the KAHA ligation is a very powerful tool for the synthesis of therapeutic peptides (30 residues) without interference from unprotected side chain functional groups. In order to explain the discrepancies between *type I* and *II* ligation (different suitable solvents and reaction concentrations) and to identify appropriate ligation partners for the synthesis of larger peptides we have elucidated the mechanism of the KAHA ligation. We found the *type I* ligation to proceed via an unexpected and remarkable pathway in which the oxygen atom of the hydroxylamine is incorporated into the amide product [2].

[1] R. M. Fox, K. D. Baucom, J. W. Bode, *Angew. Chem.* **2006**, *118*, 1270–1274; *Angew. Chem. Int. Ed.* **2006**, *45*, 1248–1252.

[2] I. Pusterla, J. W. Bode, *Angew. Chem.* **2012**, *124*, 528–531; *Angew. Chem. Int. Ed.* **2006**, *51*, 513–516.

Organic Chemistry **405**

One-Pot Synthesis of Peptide Libraries

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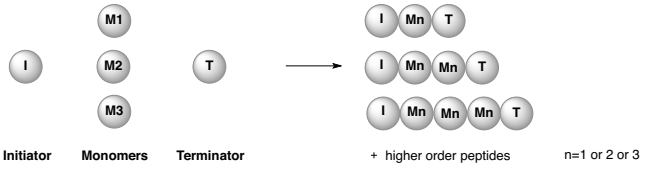
ETH-Zürich, Wolfgang Pauli Strasse 10, 8093 Zürich, Switzerland

The interest in new therapeutic peptides has increased over the past decade. Methods that can quickly be used to generate a large collection of various compounds with minimum waste and easy purification are highly desirable. We have developed a new methodology to synthesize unnatural peptide libraries in a one-pot fashion by applying chemoselecitve ketoacid-hydroxylamine (KAHA) ligation [1]. This methodology tolerates the presence of various functional groups and produces only innocuous byproducts. As the reaction condition requires no coupling reagents, the resulting peptides can be subjected to bioassay directly without further purification. Strategies for peptide library synthesis, bioactive profiling, structure deconvolution and lead optimization will be discussed.



[1] J. W. Bode, R. M. Fox, K. D. Baucom, *Angew. Chem. Int. Ed.* **2006**, *45*, 1248.

Organic Chemistry **406**

Friedel-Crafts Benzylation of Activated and Deactivated Arenes

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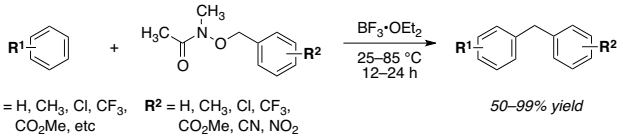
ETH Zürich, Laboratorium für Organische Chemie, Wolfgang-Pauli-Strasse 10, 8093 Zürich

The Friedel-Crafts alkylation is a versatile method for C-C bond formation from unactivated C-H bonds [1]. Despite the power and historical importance of Friedel-Crafts reactions, these processes often have major drawbacks such as their restriction to electron-rich arenes, harsh reaction conditions, low regioselectivity and the generation of large amounts of metal by-products. Therefore there is an unmet synthetic need for refinements to the Friedel-Crafts reaction to improve its substrate scope and sustainability, particularly for substitutions of electron-deficient arenes [2].



We demonstrate that *O*-benzyl hydroxamic acids are activated by the inexpensive, easily-handled Lewis acid BF_3•OEt_2 to generate highly reactive electrophiles for the Friedel-Crafts benzylation of both electron-rich and electron-poor arenes [3]. The reactions proceed at mild temperatures, are operationally and environmentally friendly, and give the product diarylmethanes in high yield. At slightly higher temperatures, electron-deficient arenes are cleanly alkylated with electron-deficent benzyl derivatives to give mono *meta*-substituted products.

[1] C. Friedel, J. M. Crafts, *Hebd. Seances Acad. Sci.* **1877**, *84*, 1450.
[2] D. J. C. Constable et. al. *Green Chem.* **2007**, *9*, 411.
[3] G. Schäfer, J. W. Bode, *Angew. Chem. Int. Ed.* **2011**, *50*, 10917.

Organic Chemistry **407**

Expanded substrate scope and catalyst optimization for the catalytic kinetic resolution of cyclic secondary amines

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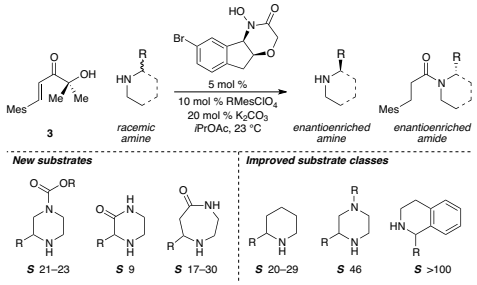
[1] ETH Zürich, Wolfgang-Pauli-Strasse 10, 8093 Zürich, Switzerland

Many pharmaceuticals and agricultural chemicals are enantiomerically pure amines. We have developed a general method for the catalytic kinetic resolution of cyclic secondary amines;[1] however, there are a few limitations to the substrates with special functional groups. New reaction conditions using a tuned hydroxamic acid co-catalyst with K_2CO_3 base in *i*PrOAc solvent have been employed to give an expanded substrate scope and an improved enantioselectivity.



[1] Binanzer, M.; Hsieh S.-Y.; Bode, J. W. "Catalytic Kinetic Resolution of Cyclic Secondary Amines" *J. Am. Chem. Soc.* **2011**, *133*, 19698–19701.

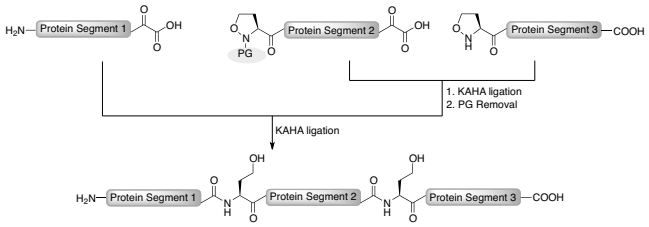
Organic Chemistry **408**

α-Ketoacid–hydroxylamine (KAHA) ligation for the chemical synthesis of modifier proteins

A. O. Ogunkoya, V. R. Pattabiraman, J. W. Bode*

Laboratorium für Organische Chemie, Wolfgang Pauli Strasse 10, ETH Zurich, 8093 Zurich, Switzerland

Recently, we developed a variation of the α-ketoacid–hydroxylamine (KAHA) ligation[1], between a C-terminal peptide α-ketoacid and a N-terminal 5-oxaproline.[2] This ligation is useful for the synthesis of proteins from two unprotected protein segments. For the synthesis of larger proteins, a sequential ligation strategy is necessary.



Our studies will show the synthesis of ubiquitin fold modier 1 (UFM1, 83 residues) through the development of a sequential KAHA ligation strategy.

[1] Bode, J. W.; Fox, R. M.; Baucom, K. D. *Angew. Chem. Int. Ed.* **2006**, *45*, 1248-1252
[2] Pattabiraman V. R.; Ogunkoya A. O.; Bode J. W. *Angew. Chem. Int. Ed.* 14 Mar.2012, D.O.I. 10.1002/anie.201200907

Organic Chemistry **409**

Kinetic Resolution of Secondary Amines with a Polymer-Supported Chiral Hydroxamic Acid

Imants Kreituss[1], Yuta Murakami[1], Michael Binanzer[1] and Jeffrey W. Bode[1]

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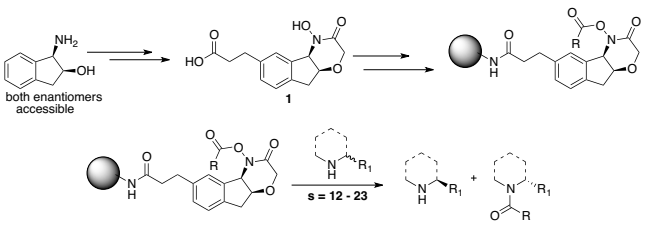
We have developed a new chiral polymer-supported hydroxamic acid for kinetic resolution of secondary amines. Carboxylic acid **1** can be prepared on a multigram scale and immobilized on the polymer support. The enantioselective resolving agent can be regenerated by a treatment of the resin with an acyl chloride or anhydride

Using this resin, various cyclic secondary amines have been resolved with good to excellent selectivities. Highly enantioenriched unreacted amines can be recovered, and there is no erosion of reactivity or selectivity after multiple uses of the reagent. The development of this convienient process for resolving racemic amines and further developments will be reported.



Organic Chemistry **410**

α,β-Unsaturated Acyl Azoliums for Enantioselective Annulations

Jessada Mahatthananchai[1] and Jeffrey W. Bode[1]

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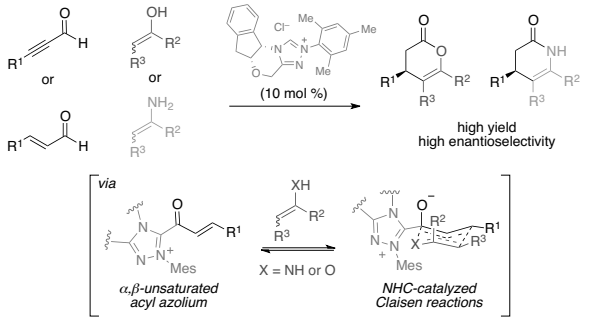
We have developed a method for the generation of α,β-unsaturated acyl azoliums from enals or ynals and a chiral N-heterocyclic carbene. These species serve as catalytically-generated activated carboxylates with a unique property. They may be intercepted by enols or enamines to generate metastable hemiacetals, which can undergo an enantioselective Claisen rearrangement and cyclization to afford dihydropyranone or dihydropyridinone in excellent yield and enantioselectivity.[1] Both the development and the mechanistic aspects of these reactions will be discussed in detail.[2]



[1] (a) J. Kaeobamrung, J. Mahatthananchai, P. Zheng, J. W. Bode, *J. Am. Chem. Soc.* **2010**, *132*, 8810–8812. (b) B. Wanner, J. Mahatthananchai, J. W. Bode, *Org. Lett.* **2011**, *13*, 5378–5381.

[2] (a) J. Mahatthananchai, P. Zheng, J. W. Bode, *Angew. Chem., Int. Ed.* **2011**, *50*, 1673–1677. (b) J. Mahatthananchai, J. Kaeobamrung, J. W. Bode, *ACS Catal.* **2012**, *2*, 494–503.

Organic Chemistry **411**

NHC-Catalyzed Enantioselective Annulation of Sulfonyl Imines and α,β-Unsaturated Aldehydes

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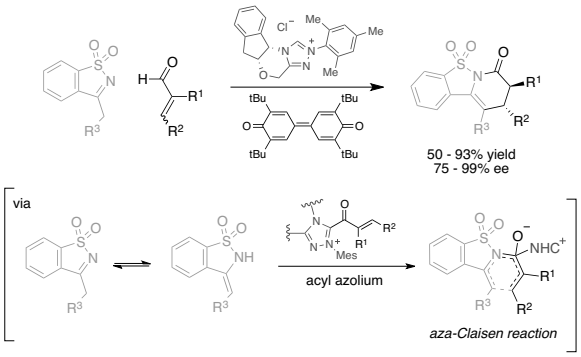
[1]Lab. für organische Chemie, Swiss Federal Institute of Technology (ETH) Zurich. Wolfgang Pauli Strasse 10, 8093 Zurich

We have developed a new enantioselective annulation of *N*-sulfonyl-imines and α,β-unsaturated aldehydes catalyzed by a chiral N-heterocyclic carbene (NHC). The catalytically-generated α,β-unsaturated acyl azolium (derived from a chiral NHC, enals, and an oxidant) undergo a reaction with the enamine tautomer of the imine via an aza-Claisen rearrangement as the key carbon-carbon bond forming step. High yields and enantioselectivities were achieved using β-substituted, α,β-substituted and β,β-disubstituted unsaturated aldehydes. This is the first example of a highly enantioselective NHC-catatlyzed annulation to operate with α-substituted enals as substrates.



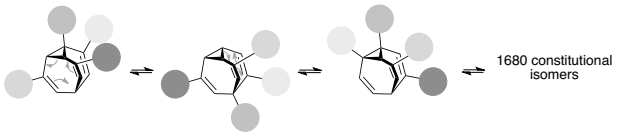
Organic Chemistry **412**

Graphical and Computational Insights into Interconversion of a Shapeshifting Molecule

Maggie He[1], Jeffrey W. Bode[1]

[1]Laboratorium für Organische Chemie, Department of Chemistry and Applied Biosciences, ETH Zürich, Wolfgang Pauli Strasse 10, 8093 Zürich, Switzerland

Bullvalene is a cage-like molecule that undergoes the Cope rearrangement spontaneously to give 1.2 million degenerate isomers [1]. Incorporation of different substituents onto the bullvalene core leads to a "shapeshifing" molecule by reorienting its substitutions as it undergoes rearrangements. A bullvalene with four different substitutions can interconvert among up to 1680 structural isomers. We have synthesized tetrasubstituted bullvalenes and conclusively demonstrated that they are robust, dynamic organic molecules [2][3]. Due to the large number of isomers, the interconversion network, which maps the rearrangements between all isomers, and the energy landscape of tetrasubstituted bullvalenes are very complex. Insights into the rearrangements of a tetrasubstituted bullvalene based on NMR studies, network analysis, and DFT calculations will be presented.



[1] W. v. E. Doering, W. R. Roth, *Tetrahedron* **1963**, *19*, 715-737.

[2] A. R. Lippert, A. Naganawa, V. L. Keleshian, J. W. Bode, *J. Am. Chem. Soc.* **2010**, *132*, 15790-15799.

[3] M. He, J. W. Bode, *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108*, 14752-14756.

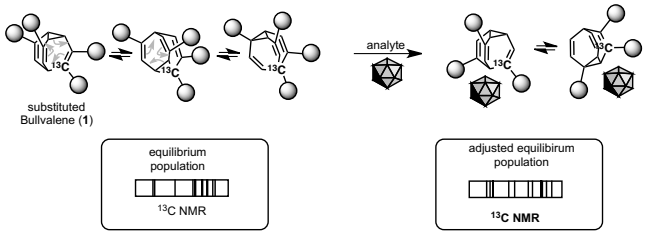
Organic Chemistry **413**

Sensor Arrays based on Shapeshifting Organic Molecules

J.F. Teichert, K.K. Larson, M. He, A. Naganawa, J.W. Bode*

Laboratorium für Organische Chemie, Department of Chemistry and Aplied Bioscience, ETH Zürich
Wolfgang-Pauli-Strasse 10, 8093 Zürich

Substituted Bullvalene compounds (**1**) exist as a mixture of rapidly equilibrating structural isomers that interconvert through spontaneous Cope rearrangements.[1] By equipping the Bullvalene core with a ^{13}C label as a reporting unit,[2] and substituents allowing for the coordination of analytes (such as fullerenes or carbohydrates),[2,3] all necessary components of a sensor are given. The read-out of the ^{13}C NMR spectrum displays the adjusted equilibrium population and distribution of the Bullvalene isomers and therefore serves as a pattern for analyte recognition.[2]



[1] A.R. Lippert, J. Kaeobamrung, J.W. Bode, *J. Am. Chem. Soc.* **2006**, *128*, 14738–14739; A.R. Lippert, A.Naganawa, V.L. Keleshian, J.W. Bode, *J. Am. Chem. Soc.* **2010**, *132*, 15790–15799.

[2] K.K. Larson, M. He, J.F. Teichert, A. Naganawa, J.W. Bode, *Chem. Sci.* **2012**, Accepted Manuscript. (DOI: 10.1039/C2SC20238G)

[3] A.R. Lippert, V.L. Keleshian, J.W. Bode *Org. Biomol. Chem.* **2009**, *7*,1529–1532.

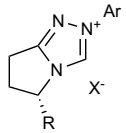
Organic Chemistry **414**

Synthesis of Bifunctional Triazolium Salts for use as N-Heterocyclic Carbenes

Chenaimwoyo A. Gondo, Annette Bahlinger, Helma Wennemers, Jeffrey W. Bode

ETH Zurich, Wolfgang-Pauli-Str. 10, 8093 Zürich Switzerland

Chiral, bicylic 1,2,4-triazolium salts, common precursors of N-heterocyclic carbenes (NHC's), have emerged as the most general class of azolium salt precatalysts for NHC-catalyzed reactions [1]. There are few synthetic routes for their preparation and modification [2]. Furthermore, the harsh conditions required for the formation of the azole ring limit the choice of additional functionality.



We have successfully prepared libraries of bifunctional triazolium salts using precursors bearing suitable functional groups and solid phase peptide synthesis. Our current efforts involve screening these catalysts for new transformations, particularly those utilizing the additional functionality to perform reactions not catalyzed by NHCs alone.

[1] D. Enders, O. Niemeier, A. Henseler *Chem. Rev.* **2007**, *107*, 5606
[2] C. A. Gondo, J. W. Bode, *Science of Synthesis*, **2012**, *13.33*

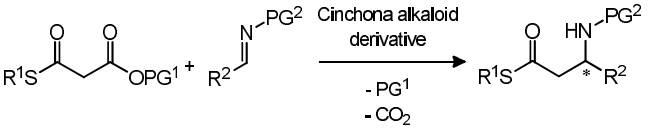
Organic Chemistry **415**

Cinchona Alkaloid Catalyzed Mannich Reactions of Mono Thiomalonates with Imines for the Synthesis of β-aminothioesters

Annette Bahlinger[1,2] and Helma Wennemers[2]

[1]Department of Chemistry, University of Basel, St. Johanns-Ring 19, CH-4056 Basel, Switzerland
[2]Laboratory of Organic Chemistry, ETH Zürich, Wolfgang-Pauli-Strasse 10, CH-8093 Zürich, Switzerland

The stereoselective synthesis of β-aminothioesters is of high interest since they are common chemical building blocks for a variety of pharmaceutical important compounds.[1] An attractive way to generate thioesters in general, is the use of thioester enolates. Due to the low acidity of their α-protons, thioester enolate generation typically requires harsh conditions.[2] Recently our group introduced mono thiomalonates (MTMs) as thioester enolate-equivalents allowing for mild organocatalytic conditions in 1,4 addition reactions with nitroolefins.[3]



Herein we show that also imines react readily with MTMs. The addition products, β-aminothioesters, were obtained in excellent yields (up to 99%) and stereoselectivities (up to 98% ee) using only 1 mol% of a cinchona alkaloid derivative. Furthermore we present β-aminothiosters as pre-activated β-amino acids that can easily be used for β-peptide synthesis.

[1] T. Miyazaki, Y. Han-ja, H. Tokuyama, *Synlett* **2004**, 477.
[2] F. G. Bordwell, *Acc. Chem. Res.*, **1988**, *21*, 456.
[3] P. Clerici, H. Wennemers, *Org. Biomol. Chem.*, **2012**, *10*, 110.

Organic Chemistry **416**

Peptide-catalyzed Stereoselective Construction of γ-Nitroaldehydes Bearing a Quaternary Stereogenic Carbon Center

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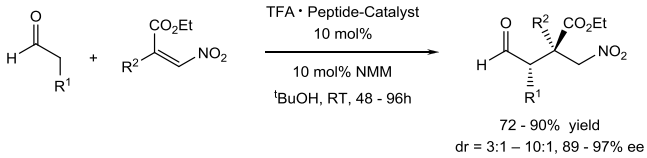
Laboratorium für Organische Chemie, ETH Zürich
Wolfgang Pauli-Strasse 10, 8093 Zürich, Switzerland

The conjugate addition reaction of aldehydes to nitroolefins is an important reaction that provides synthetically useful γ-nitroaldehydes. Our group successfully introduced tripeptides of the type Pro-Pro-Xaa (Xaa = acidic amino acid) as highly efficient catalysts for asymmetric conjugate addition reactions of aldehydes to β-mono- and α,β-disubstituted nitroolefins [1][2]. Furthermore, we became interested in using β,β-disubstituted nitroolefins as electrophiles since they would afford the corresponding γ-nitroaldehydes with a quaternary stereogenic carbon center. Their construction is challenging as β,β-disubstituted nitroolefins are significantly less reactive compared to β-monosubstituted nitroolefins due to their increased steric demand.



Here, we show the peptide-catalyzed stereoselective conjugate addition reaction of different aldehydes to β,β-disubstituted nitroolefins providing γ-nitroaldehydes bearing a quaternary stereogenic center in good yields and stereoselectivities.

[1] a) M. Wiesner, J. D. Revell, H. Wennemers, *Angew. Chem. Int. Ed.* **2008**, *47*, 1871-1874. b) M. Wiesner, G. Upert, G. Angelici, H. Wennemers, *J. Am. Chem. Soc.* **2010**, *132*, 6-7. c) M. Wiesner, M. Neuburger, H. Wennemers, *Chem. Eur. J.* **2009**, *15*, 10103-10109.
[2] J. Duschmalé, H. Wennemers, *Chem. Eur. J.* **2012**, *18*, 1111-1120.

Organic Chemistry **417**

Construction of Acyclic Quaternary All-Carbon Stereogenic Centers with α-Substituted Mono Thiomalonates

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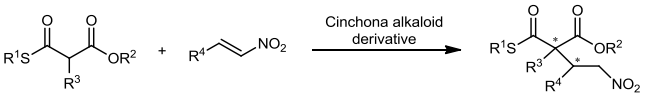
[1]ETH Zürich, Wolfgang-Pauli Strasse 10, CH-8093 Zürich, Switzerland

Quaternary stereogenic centers bearing four different carbon substituents are present in many important pharmaceuticals and naturally occurring compounds. Catalytic asymmetric C-C bond forming reactions that generate such all-carbon quaternary centers are therefore highly valuable in organic synthesis.[1] However, their successful development has proven rather challenging, especially in the case of acyclic stereocenters.[1] We report the highly efficient and stereoselective catalytic generation of quaternary all-carbon stereogenic centers in acyclic system by means of the novel prochiral nucleophile, mono thiomalonates (MTMs)[2] having a carbon substituent at the α-position.



In the presence of small amounts of bifunctional cinchona alkaloid organocatalysts (2-6 mol%), α-substituted MTMs smoothly reacted with β-nitroolefins to afford synthetically valuable α-quaternary γ-nitrothioesters in excellent diastereoselectivities (≈ 10:1) and enantioselectivities (up to 99% ee).

[1] For a review, see: J. P. Das, I. Marek, *Chem. Commun.*, **2011**, *47*, 4593.
[2] P. Clerici, H. Wennemers, *Org. Biomol. Chem.*, **2012**, *10*, 110.

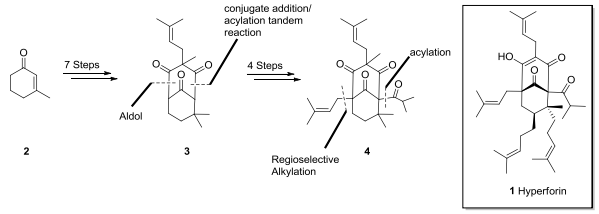
Organic Chemistry **418**

Straightforward synthesis to Hyperforin analogues

Isak Alimi, Michael Bersier, Christian. G. Bochet

University of Fribourg, Ch. du musée 9, CH-1700 Fribourg

Due to its structural complexity and biological activity, Hyperforin **1** has emerged as a challenging target for total synthesis. The first total synthesis of the *ent*-Hyperforin has been reported only recently by Shibasaki *et al* [1].



Scheme 1 : 11 steps sequence to hyperforin analogue **4**

Our efforts towards the total synthesis of Hyperforin **1** are focused on the formation of the bicyclo[3.3.1]nonane core **3.** The synthesis of Hyperforin analogue **4** was achieved in 11 steps starting from cyclohexanone **2** [2].This straightforward route shows also flexibility by the possibility of installing other functionalities on methylcyclohexenone **2,** which could lead to the synthesis of other PPAP's natural products like Clusianone or Nemorosone.

[1] Shimizu, Y.; Shi, S.-L.; Usuda, H.; Kanai, M.; Shibasaki, M., *Angew. Chem. Int. Ed.* **2010,** *49*, 1103-1106.
[2] a) Ahmad, N. M.; Rodeschini, V.; Simpkins, N. S.; Ward, S. E.; Blake, A. J., *J. Org. Chem.* **2007,** *72*, 4803-4815. b) Siegel, D. R.; Danishefsky, S. J., *J. Am. Chem. Soc.* **2005,** *128*, 1048-1049.

Organic Chemistry **419**

Asymmetric photochemical synthesis by kinetic resolution using chiral quenchers

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Department of Chemistry of Fribourg,
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There are two ways of promoting a photochemical reaction: the excitation by direct irradiation and the indirect excitation by sensitization. In the direct excitation mode, a singlet is the first obtained, which can then evolve into a triplet state, if the intersystem crossing is faster than the reaction. For the indirect excitation, the excited state is obtained using sensitizer. If a chiral sensitizer is used, there is a possibility of obtaining the product of the photochemical reaction with a certain enantiomeric excess.[1, 2] The principal problem for the modest results published so far in the literature is the weak interaction between the substrate and the chiral sensitizer and the short lifetime of the excited state.

The aim of our project is to use a quencher instead a sensitizer. In the presence of a chiral triplet quencher, an enantiomeric excess could be in principle obtained by kinetic resolution: the triplet quencher deactivates only one of the enantiomers of the racemic triplet state. For an optimal interaction and selectivity between the substrate and the chiral quencher, we use a host-guest principle. In this work, we will show our first results on the intramolecular photocycloaddition of racemic enones.

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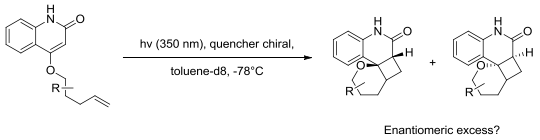

Organic Chemistry **420**

Conditional Triggered Drug Release

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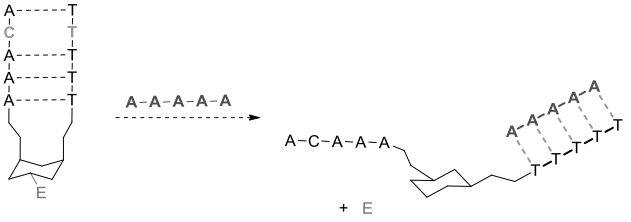
Nowadays, the need of internal fixation devices or joint replacement is dramatically increasing, which means also increasing percentages of infections. The solution to this problem was until now to cover the implant with a coating of antimicrobial agent. Unfortunately the constant presence of antibiotics leads often to bacterial resistance and the coatings quick aging implicate a replacement.

We propose encapsulated antimicrobial agent with a trigger system to open the capsules only in presence of bacteria as a solution to the actual situation.

We are currently synthesizing a trigger system composed of a cyclohexane ring kept in an unstable conformation with two almost complementary oligonucleotide strands. The mismatch present in the two DNA strands should allow a conformational change in presence of fully complementary bacterial RNA strand. With this conformational change, two functional groups should undergo a chemical reaction and release a leaving group that is responsible for the opening of the capsules liberating the antimicrobial agent. This poster will focus on the synthesis of the central core and the side linkers.



Organic Chemistry **421**

Synthetical approaches to investigate proteins-chemical warfare agents adducts

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[2]Spiez Laboratory, CH-3700 Spiez

Unequivocal methods to verify exposure to chemical warfare agents (CWAs) give credibility to the verification regime of the Convention on the Prohibition of the Development, Production, Stockpiling and Use of Chemical Weapons and on their Destruction.[1] Because of their stability and their specificity, adducts formed between CWAs and proteins are good candidates as biomarkers for the analytical investigation.[2] Furthermore, these adducts can give important indications about the CWAs' actions in the body.

Our goal is to synthesize a library of potential amino acids-CWAs adducts [3, 4, 5] that could be then incorporated in Solid Phase Peptides Synthesis affording reference standards for their unambiguous identification. Their stability in physiological medium will be tested to determine if there is a chance to recover them from contaminated biological samples, such as blood and urine. Relevant biomarkers will be so identified for the development of analytical methods. In this contribution, we will show the first results about adducts' synthesis, especially for organophosphonates CWAs.

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Organic Chemistry **422**

Exploiting Rh(I)-Rh(III) Cycles in Enantioselective Strain-promoted C–C Bond Cleavages

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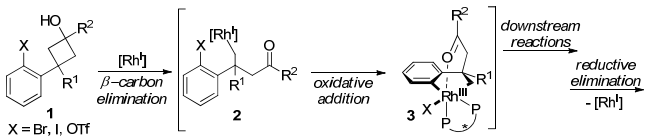
BCH 4305, CH-1015 Lausanne, Switzerland

Small ring substrates play an important role for C–C σ-bond activations as their inherent ring strain facilitates metal insertion.[1] Our group reported rhodium-catalyzed enantioselective β-carbon eliminations from *tert*-cyclobutanols giving rise to alkyl rhodium intermediates bearing an all-carbon quaternary stereogenic center. This key intermediate enables access to a diverse range of products via a number of different downstream reaction pathways.[2] So far, these pathways did not involve redox chemistry of rhodium as all transformations proceed consistently with Rh(I) complexes. However, redox processes could greatly diversify the accessible product range. Towards this goal, we envisioned that alkyl rhodium intermediate **2** might undergo an oxidative addition with an appended aryl halide to form a rhodium(III) species **3**. We report downstream pathways of **3** giving rise to new product branches in high enantioselectivities.



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Organic Chemistry **423**

Highly Substituted 1-Indenylamines by Rhodium(I)-Catalyzed Directed C-H Activations

Duc N. Tran, Nicolai Cramer

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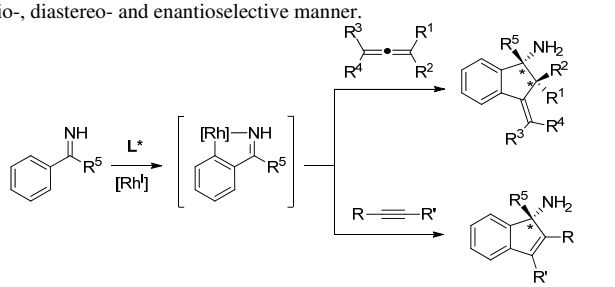
The activation of inert carbon-hydrogen bonds is a powerful, yet very challenging tool to streamline synthesis. Using this approach, complex structures might be rapidly accessed from simple starting materials without the requirements of prefunctionalization.[1] Our research focuses on the development of C-H activation processes using synthetically versatile directing groups capable of participating in a cascade reaction.[2] Such processes provide an additional handle to increase diversity and molecular complexity of the formed products. We report hereby our recent progress in using free ketimines as participative directing group in rhodium(I)-catalyzed C-H functionalization providing access to heavily substituted 1-indenylamines in a regio-, diastereo- and enantioselective manner.



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Organic Chemistry **424**

A Rapid and Modular Access to Arylsultams by Rh(III)-Catalyzed C-H Activation

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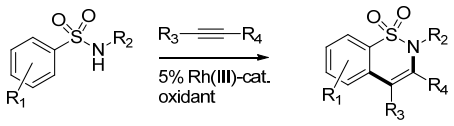
The sulfonamide group is a classical and important pharmacophore in medicinal chemistry. Arylsultams represent as well an important motif due to their wide range of biological activities.[1] Several methods and strategies to synthesize sultams have been reported. However, all of them require several steps from commercially available materials and/or functionalized substrates.[2]

Directed C-H bond activations have recently attracted significant attention because of their efficiency and atom economical alternative to classical synthesis.[3] In this respect, several new Rh(III)-catalyzed processes have emerged over the past years.[4] We report our findings on applying Rh(III)-catalyzed C-H activation of arylsulfonamide derivatives and their subsequent cyclisation with internal alkynes to provide an efficient and highly yielding route to arylsultams.



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Organic Chemistry **425**

Application of chiral Cp-ligands in asymmetric Rh(III)-catalyzed C-H activations

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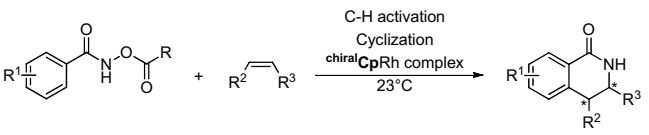
EPFL SB ISIC LCSA, CH-1015 Lausanne, Switzerland

Cyclopentadienyl (Cp) and pentamethylcyclopentadienyl (Cp*) ligands are of fundamental importance in organometallic chemistry and as well in catalysis. Although chiral analogs of Cp-ligands are known, there are only scarce applications in catalysis. [1] Despite their high potential, asymmetric reactions with late transition metal complexes, where the sole source of chirality stems from in the Cp fragment, are completely elusive. Recently, a particular interest in Cp*M (M = Rh, Ir, Co) complexes arose from their activity as C-H activation catalysts.

We have elaborated a facile and flexible synthesis of a new class of enantiopure C_2-symmetric Cp ligands. To showcase their utility, the corresponding rhodium complexes were applied in the first asymmetric version of isoquinolinone synthesis. [2] The chiral Cp-Rh complexes demonstrate high reactivity, delivering the products with excellent regio- and enantio-control.



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Organic Chemistry **426**

Enantioselective Hydrocarbamoylation Approach towards Substituted γ-Lactams

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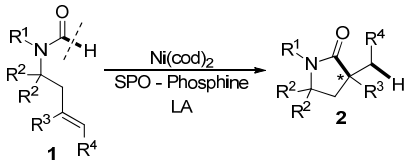
EPFL SB ISIC LCSA, CH-1015 Lausanne, Switzerland

Nickel/phosphine/Lewis-acid (LA) catalyzed hydrocarbamoylation of unsaturated bonds, formally constituting a simultaneous carbamoyl and hydrogen transfer of a formamide group, [1] provides a direct and an atom-efficient route to a range of substituted amides. The intramolecular reaction of readily accessible homoallylamine formamides **1** leads to chiral γ-lactams **2**. However, despite the abundance and wide use of chiral phosphines as ligands for transition metal catalysis, no enantioselective examples of this useful transformation have been described so far.
We have developed a novel highly co-operative catalytic system comprised by a phosphine and a chiral secondary phosphine oxide (SPO) in combination with an activating LA, which is considerably more efficient, than phosphine-only systems. The modular SPO-phosphine combination affords various γ-lactams with high yields and good enantioselection.



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Organic Chemistry **427**

Radical Carboazidation Reaction with Iodomethyl Sulfones

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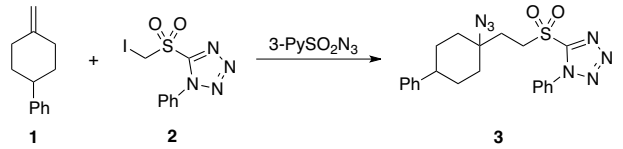
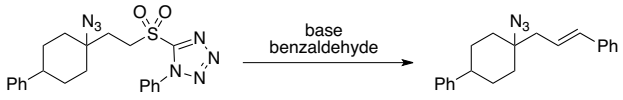
Renaud et al. developed a radical carboazidation reaction [1] that formed a carbon-carbon bond and a carbon-nitrogen bond at once. This method was performed with α-iodo esters and was applied to the total synthesis of natural products as monomorine I [2] and lepadiformine [3]. The scope of the carboazidation reaction was now extended to iodomethyl sulfones.



1 2 3

The introduced 1-phenyl-1*H*-tetrazole-5-yl group give the possibility for performing a Julia-Koscienski olefination [4].



3 4

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Organic Chemistry **428**

Toward the Total Synthesis of Aignopsanoic Acid A

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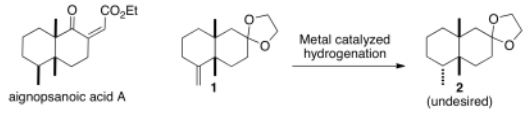
[2]University of Barcelona, *Av. Joan XXIII sn, 08028 Barcelona, Spain*

Aignopsanoic acid A, exhibiting a moderate activity against *Trypanosoma brucei*, has been isolated in 2009 from *Cacospongia mycofijiensis* [1]. Two features were identified as key steps in its synthesis: the all-*cis* configuration of the methyl groups on the readily available Wieland-Miescher ketone [2] framework and the introduction of the missing carbonyl on the side chain.



Facing the failure of the metal catalysed hydrogenation of intermediate **1** to afford the desired stereoisomer [3], we turned our attention to the hydroboration. We will present a new approach based on hydroboration and direct protonolysis [4] yielding selectively the all-*cis* stereoisomer.

We then focused on the second key step: the introduction of a single carbon atom on an unactivated double bond. Strategy featuring a formal radical mediated Karash addition will be described.

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Organic Chemistry **429**

Preparation of the Mitomycin Tricyclic Core via a Diastereoselective Radical Cascade

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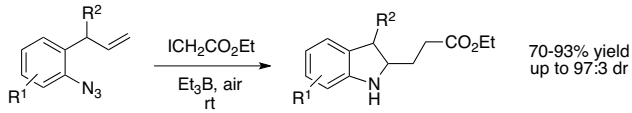
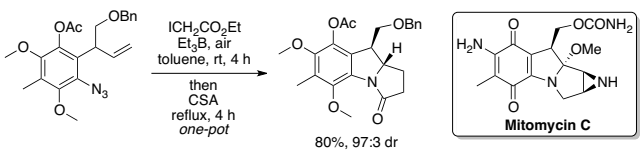
Radical chemistry is a powerful tool to create carbon-heteroatom bonds and carbon-nitrogen bonds are readily formed when organic azides are used as radical traps.[1] As part of our ongoing interest in the field of radical processes involving azides and alkaloid synthesis, a novel mild approach to prepare indolines via a tandem radical addition/cyclization onto *ortho*-azidoallylbenzenes will be described.



The mitomycins are an important class of bioactive natural products exhibiting potent anticancer properties.[2] Our radical cascade allowed us to access their tricyclic core structure in a highly diastereoselective manner.



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Organic Chemistry **430**

Addition of Mono-organocopper Reagents to Thioiminium Ions

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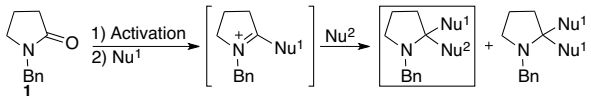
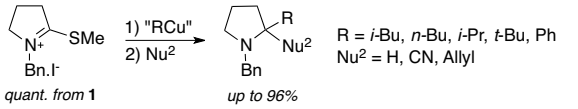
Universität Bern, *Departement für Chemie und Biochemie*, Freiestrasse 3, CH-3012 Bern, Switzerland

In alkaloids synthesis, the creation of quaternary stereogenic centers by *gem*-dialkylation of lactams is a attractive but still a challenging task. The methods developed to achieve this transformation involve, after an initial activation step, the successive addition of two nucleophiles.[1] However, the iminium intermediate which is formed upon addition of the first nucleophile is usually more reactive than the activated lactam and, in such conditions, the symmetrical *gem*-dialkylation side-product cannot be avoided.[2]



We report here that with thioiminum ions, the use of mono-organocopper reagents as first nucleophiles offers a new approach, allowing the clean formation of non-symmetrical products. Our progresses towards more elaborated structures will also be disclosed.



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Organic Chemistry **431**

α-Chloro *B*-alkylcatecholboranes as Radical Precursors

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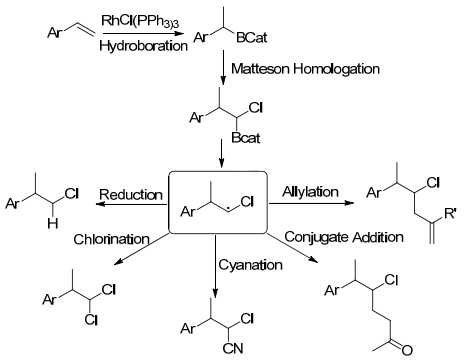
B-alkylcatecholboranes have been shown to be efficient alkyl radical precursors [1]. We have developed a one-pot radical procedure involving α-chloro *B*-alkylcatecholboranes which were generated from vinyl arenes via hydroboration with catecholborane followed by Matteson homologation [2] [3]. The new α-chloro *B*-alkylcatecholboranes can be employed in a wide range of reactions, such as allylation, reduction, chlorination, cyanation and conjugate addition to unsaturated ketones.



This procedure also provides a potential approach to introduce –CClX groups onto alkenes.

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Organic Chemistry **432**

Templated Self-Sorting in Self-Organizing Surface-Initiated Co-Polymerization

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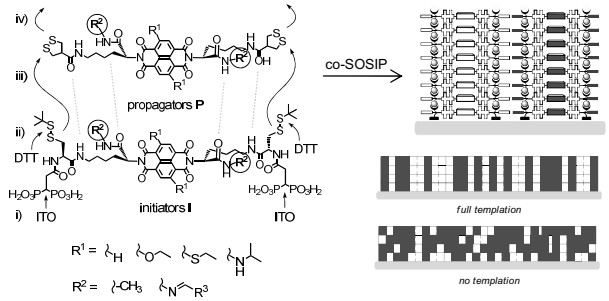
University of Geneva, Department of Organic Chemistry, 30 Quai Ernest Ansermet 1211 Geneva 4, Switzerland

Recently we have invented self-organizing surface-initiated polymerization (SOSIP) as promising way to provide facile access to ordered and oriented multicomponent architectures on surfaces [1]. The stacking of naphthalenediimides (NDIs) cores in SOSIP architectures offers electron/hole transporting channels, which can also be further developed to multichannel architectures with multicomponent gradients [2,3]. Our current studies are directed to precise control of self-sorting by templated-directed co-SOSIP. Topology and π-acidity of SOSIP initiators/propagators determine sorting and templation efficiency. Furthermore, tuning of side-chains is also expected to be an additional element for regulating the surface-templation effect and property of multicomponent photosystems.



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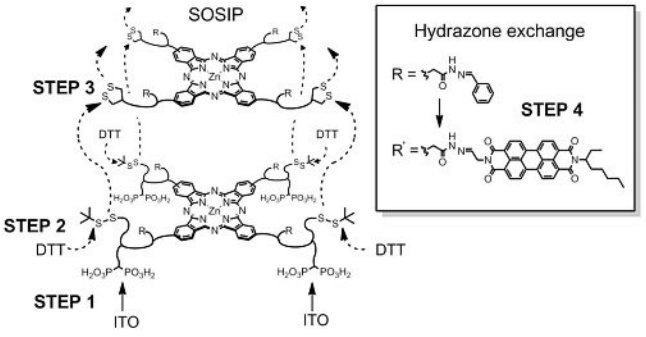
Organic Chemistry **433**

Coaxial Multichromophoric Photosystems

Giuseppe Sforazzini, Naomi Sakai, Stefan Matile*

University of Geneva, Department of Organic Chemistry, 30 Quai Ernest Ansermet, 1211 Geneva 4, Switzerland

Here we report preparation of multichromophoric coaxial charge-transport architectures consisting of phthalocyanine (Pc) and perylenediimide (PDI). A rationally designed Pc containing structurally supporting peptide side-chains, hydrazides, polymerizable disulfides and diphosphonate anchoring groups was covalently bound onto the ITO surface. Self-organizing surface-initiated polymerization (SOSIP) was used to build vertically aligned Pc assembly (*p*-type channel) covalently linked by disulfide bonds. Hydrazone exchange of benzaldehydes with PDI aldehydes introduces an outer vertical electron-transporting pathway (*n*-type channel).[1] The proposed bottom-up approach affords formation of well-organized vertical charge-transport coaxial architectures which have large interest in the optoelectronics field.



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Organic Chemistry **434**

Cell-Penetrating Peptides (CPPs) with Disulfide Bonds

Oleksandr Kucherak, Eun-Kyoung Bang, Stefan Matile*

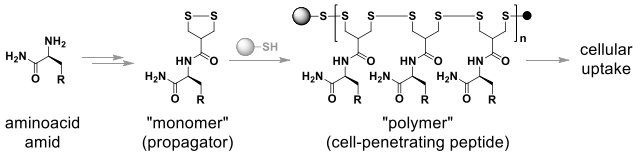
University of Geneva, Geneva, Switzerland

Since the discovery in 1988, cell-penetrating peptides (CPPs) gained a great potential as delivery vectors for use in research and medicine. While designing a CPP-molecule, the dynamic covalent bonds can be used [1].

Our research is focused on the development of CPPs containing the amino-acid molecules, functionalized with asparagusic acid moiety. The latter includes a disulfide bond that plays the crucial role due to easiness of its formation and cleavage: desired peptide can be obtained by polymerization reaction, and after uptake it can be easily degraded inside a cell.

Variation of CPPs' composition by copolymerization opens a road to the library of potential synthetic delivery vectors. The exploration of uptake-activities of newly synthesized peptides is done in lipid vesicles by fluorescence assays [2,3] and the most active samples will be further used for experiments in live cells.

The obtained results will extend current knowledge on the nature of CPP-uptake process and may result in an invention of the efficient delivery toolkit for wide applications both in science and medicine.



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Organic Chemistry **435**

Asymmetric Imine Aziridination with Ru/PNNP: Anion Tuning

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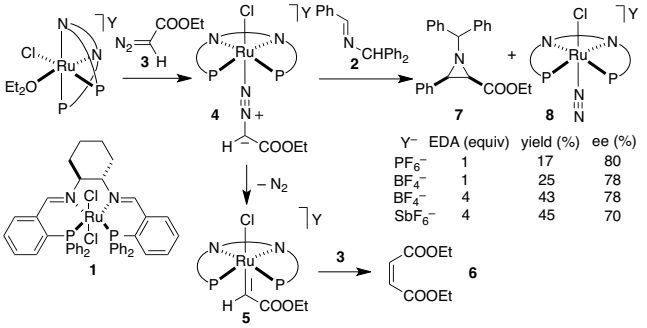
Our group has reported[1] that $[RuCl_2(PNNP)]$ (**1**), after activation with $(Et_3O)PF_6$ (1 equiv), catalyzes the asymmetric aziridination of imine **2** with ethyl diazoacetate (**3**) with the intermediacy of the diazoester complex **4**. The latter species either transfers carbene to the imine or decomposes to the carbene complex **5** that reacts with **3** to give diethyl maleate (**6**), hence lowering the yield of aziridine **7**.



We find now that, by changing the anion from PF_6^- to BF_4^- or SbF_6^-, the aziridine yield improves with little impact on the enantioselectivity in the case of BF_4^-, and reaches 45% with an excess of **3** (4 equiv). Interestingly, running the reaction in a closed vessel, in which N_2 pressure builds up, reduces the yield of aziridine to 32% under the same conditions, in agreement with the accumulation of the dinitrogen complex **8**.

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Organic Chemistry **436**

Force Fields for Energetics and Dynamics of Organometallic Complexes and Applications

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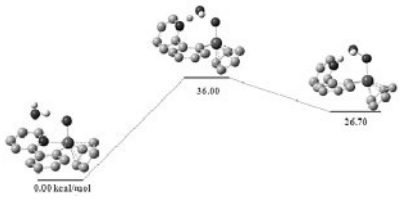
The development of transition metal catalysts requires an accurate way to predict relative energies and activation barriers for multiple diastereomers. A fast approach is VALBOND TRANS[1] (VBT) which is based on valence bond theory and includes the trans influence of ligands on bond lengths and relative energies. In the present contribution, the VBT force field is generalized for model octahedral complexes containing Ir, so that DFT relative energies for different diastereomers can be reproduced. For this, the point charges and the vdW parameters[2] were fitted with INolls[3]. To examine the transferability of the parameters, the homogeneous oxidation reaction of water[4] to dioxygen was investigated with VBT. Transition states were modeled with adiabatic reactive MD[5] to qualitatively reproduce three different mechanisms, which were already suggested by DFT calculations[4].



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Organic Chemistry **437**

Asymmetric Hydrogenation of α,β-Unsaturated Esters using Chiral Iridium P,N Catalysts

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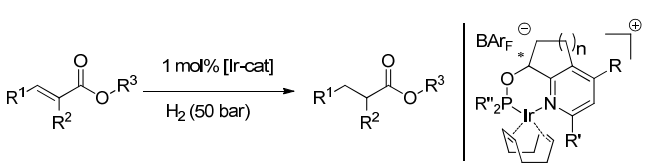
Enantioselective conjugate reductions represent one of the most widely-used reaction types in metal catalyzed asymmetric catalysis.[1] However there are only few studies on the reduction of trisubstituted α,β-unsaturated esters in literature and especially for α-substituted substrates high selectivities are hard to be obtained.[2] In 2010 we reported the first highly enantioselective reductions of α-substituted α,β-unsaturated esters using chiral pyridyl phosphinites with large aryl substituents as ligands.[3] Based on this results we tested several substitution patterns to get a closer insight into the substrate scope and a better understanding in the applicability and performance of these catalysts.



Herein we disclose expanded results in the hydrogenation of α,β-unsaturated esters and observations with the used catalyst systems.

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Organic Chemistry **438**

Synthesis and properties of linear and macrocyclic azocarbazoles

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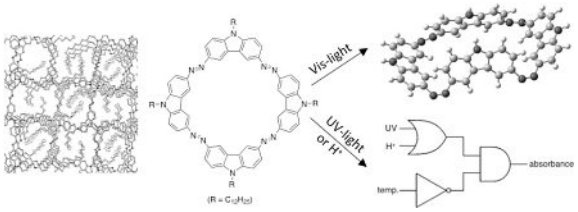
Azo compounds are well known for their application as dyes. In the last years, research has broadened their use for advanced materials [1]. The incorporation of azo units is a common approach to realize switches on a molecular level [2]. In this work an azocarbazole macrocycle with π-conjugation and four azo units was synthesized and its photochemical properties investigated. This molecule combines the properties of a shape-persistent macrocycle and the special electronic features of carabazole units with the potential of a molecular switch. NMR measurements in the photostationary state, UV-spectroscopy and x-ray crystallography were used for characterization of the complex properties. It was found that irradiation with visible light led to isomerization. Whereas, irradiation with UV-light in a chlorinated solvent led to the photo-formation of HCl and protonation of the azocarbazole. The wide range of qualities makes azocarbazoles suitable for the application as integrated molecular logic gates.



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Organic Chemistry **439**

Lewis Acid Catalysed Inverse Electron-Demand Diels-Alder Reaction – A New Synthetic Entry to Steroids

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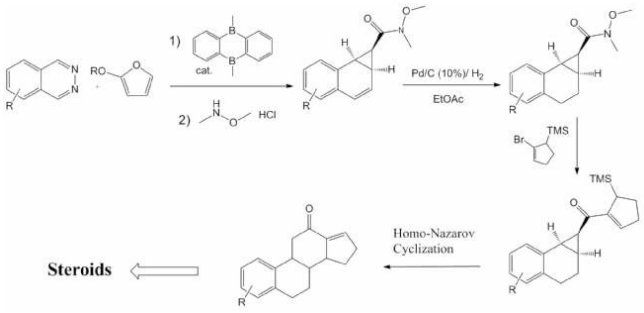
A highly functionalized cyclopropanated naphthalene is easily accessible in one step via a domino inverse electron-demand Diels-Alder (IEDDA)-cyclopropanation reaction catalysed by a bidentate Lewis acid [1]. This intermediate can be transformed [2] to a precursor ideally suited for a homo-Nazarov cyclization [3] yielding directly the 6-6-6-5-tertacyclic steroid ring system. This strategy provides a straightforward access to steroids, i.e. estrogens as potential anticancer agents, which are difficult to prepare by standard steroid functionalization procedures.



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Organic Chemistry **440**

Bidentate Lewis Acid Catalysis: A New Entry to Highly Substituted Naphthalenes

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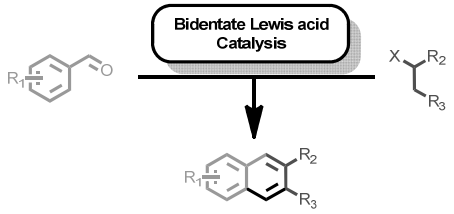
Multidentate interactions are the secret to nature's catalysis. Nonetheless the application of these principles remains an extremely challenging endeavor. In organic synthesis the Lewis acid catalysis presents a very effective tool for a variety of different transformations. Although effort has been made towards bidentate Lewis acid catalysts still they react in a monodentate fashion.[1] Recently, we were able to show the catalysis of the inverse electron-demand Diels-Alder (IEDDA) reaction of 1,2-diazines by a bidentate Lewis acid in a bidentate fashion.[2] The general principle is based on the following rational: The twofold coordination of the bidentate Lewis acid to the 1,2-diazine decreases the energy level of the LUMO facilitating the cycloaddition step. Consecutive elimination of N_2 generates the product and also liberates the catalyst.



This new concept of catalysis is furthermore combined with a novel one-pot synthesis of 1,2-diazino aromatics to produce highly substituted naphthalenes in two steps from aromatic aldehydes.

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Organic Chemistry **441**

Triangulene-derived Push-Pull Chromophores

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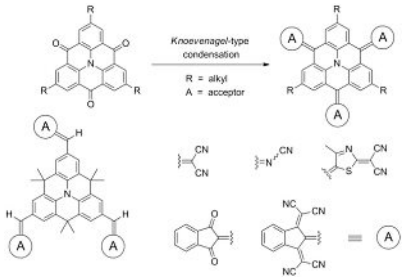
Push-pull chromophores consisting of strong donor and acceptor moieties connected through π-conjugating linkers have attracted much attention due to their strongly bathochromically shifted UV/vis absorption bands as absorbers in bulk heterojunction organic solar cells or as functional dyes for nonlinear optics [1].



Scheme 1: Synthesis of the triangulene push-pull chromophores by *Knoevenagel*-type condensation of CH-acidic acceptors (A) with the corresponding carbonyl precursors.

Bridged triphenylamine derivatives, so-called triangulenes, have been realized by *Hellwinkel* and co-workers about 40 years ago [2]. However, the potential of these scaffolds for the construction of π-systems with interesting optoelectronic properties have by far not been exhausted to date. Here, we present the synthesis and optoelectronic properties of a series of novel triangulene chromophores featuring intramolecular charge-transfer interactions.

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Organic Chemistry **442**

Probing the Mechanism of Post-lesion DNA Bypass Using 3' Synthetic Base Modified Primers

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DNA mutations can arise from errors during polymerase-mediated DNA replication; for example during translesion DNA synthesis (TLS). TLS involves specialized polymerases (Y-family DNA polymerases) that replicate past replication-blocking DNA lesions. Currently many studies investigate the mutagenic profile of nucleoside triphosophate incorporation opposite DNA lesions while less has been studied regarding the extension immediately following lesion bypass, i.e. post-lesion DNA synthesis (PLS). In this study the model bulky DNA lesion O^6-Benzylguanine (O^6-BnG) and Dpo4, a TLS polymerase, was used to investigate molecular level details of PLS. Structure activity relationships were probed using a series of 3' modified primers that paired opposite O^6-BnG to investigate the ability of Dpo4-mediated primer extension. Data regarding single nucleotide incorporation, full length primer extension, steady-state kinetic incorporation efficiencies, and computational modeling of synthetic base modified primers within the active site of Dpo4 will be presented.

Organic Chemistry **443**

Nucleoside Probes for Detecting O^6-Alkyl-2'-deoxyguanosine in DNA

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[1]ETH Zürich, Institute of Food, Nutrition, and Health

Alkylation of DNA to form nucleoside adducts is an important transformation leading to mutagenesis and carcinogenesis. A possible means for detecting DNA adducts are hybridization probes, which are oligonucleotides containing nucleoside analogs designed to pair opposite specific adducts, such as O^6-alkyl-2'-deoxyguanosine (O^6-alkyl-dG). Alternatively, polymerase-mediated amplification of adducted DNA to facilitate detection would be desirable. We have evaluated a series of nucleoside analogs for utilization in both hybridization probes and for polymerase-mediated incorporation opposite O^6-alkyl-dG adducts. Results indicate that nucleoside analog size, shape, pi-stacking ability, and hydrogen bonding capacity influence selectivity and effectiveness in hybridization and DNA synthesis.

Organic Chemistry **444**

Using Selenocysteine Substitutions to Steer Oxidative Protein Folding

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Bovine pancreatic trypsin inhibitor (BPTI) is a small protein comprised of 58 amino acids and three disulfide bonds. Its folding mechanism has been extensively studied.[1] We anticipated that substituting cysteine residues in BPTI with selenocysteine might steer the oxidative folding of the protein, since the greater stability of selenosulfide and diselenide bonds compared to disulfides can be exploited to populate specific intermediates. In addition, given the ability of small molecule diselenides to catalyze oxidative protein folding, judiciously positioned Sec residues in BPTI could conceivably enhance folding efficiency.[2] To test these ideas, we chemically synthesized several BPTI analogues containing Sec at key positions (5, 14, 30 and 38) using solid-phase peptide synthesis and native chemical ligation methods.[3] These procedures were then applied to the preparation of the wildtype and selenium-containing BPTI variants. The effects of selenium incorporation on the folding of BPTI will be discussed.[4]

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[2] a) J. Beld, K. J. Woycechowsky, D. Hilvert, *J. Biotechnol.* **2010**, *150*, 481-489; b) J. Beld, K. J. Woycechowsky, D. Hilvert, *Biochemistry* **2007**, *46*, 5382-5390; c) J. Beld, K. J. Woycechowsky, D. Hilvert, *Biochemistry* **2008**, *47*, 6985-6987; d) N. Metanis, C. Foletti, J. Beld, D. Hilvert, *Isr. J. Chem.* **2011**, *51*, 953-959.
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Organic Chemistry **445**

Directed Evolution of *Escherichia coli* K12 Transketolase A for Improved Thiamin Pyrophosphate Analogs Binding

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Transketolase is a key thiamin-dependent enzyme in the pentose phosphate pathway for the synthesis of ribose. Its inhibition has been reported as a treatment for cancer [1] and a deficiency impairs the central nervous system [2]. The enzyme from *E. coli* is a well-studied and characterized protein [3][4]. Mutations of specific residues of the active site were performed to investigate the binding of thiamin pyrophosphate analogs. We have used a Benzyl thiazolium derivative and shown that it can be pyrophosphorylated with Thiamin pyrophosphokinase. In this poster results will be presented showing the activity of this and other thiamin analogs with the modified Transketolases. This work opens up possibilities for developing a range of novel, unnatural cofactor-dependent enzymes.

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Organic Chemistry **446**

Exploration of Capsid Dynamics by Photoisomerizable Protein Modification

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Laboratory of Organic Chemistry, ETH Zürich, 8093 Zürich, Switzerland

Lumazine synthase (LS) from the hyperthermophilic bacterium *Aquifex aeolicus* is a nonviral protein that forms capsid-like structures consisting of 60 or more subunits. Engineered LS variants have previously been shown to have great potential as protein containers for encapsulating macromolecules.[1] One of these variants (AaLS-13) was optimized by directed evolution to encapsulate positively charged proteins.[2] It exhibits high loading capacity *in vitro*, but interestingly, unlike wild type LS, it displays two distinctive states corresponding to the pentamer and capsid structures. Further analysis revealed that unusual structural dynamics exist between these two states.[3] However, the mechanistic details have remained elusive. To explore this dynamical feature, we investigated the effects of chemical modification on the quaternary structure of the capsid using various thiol-reactive reagents. In addition, we designed to incorporate a phosoisomerizable azobenzene moiety into the protein to alter or control the structural dynamics by light. The azobenezene moiety can be either chemically introduced on the mutated cysteine residue or genetically incorporated using an orthogonal tRNA–amino-acyl tRNA synthetase pair.[4] Successful photocontrol of the capsid dynamics is an attractive strategy for encapsulation/release of cargo for various future applications.

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Organic Chemistry **447**

Structure and Function of Computationally Derived Enzymes

Daniel M. Pinkas[1], Rebecca Blomberg[1], Hajo Kries[1], Peer R. E. Mittl[2], Markus Grütter[2], and Donald Hilvert[1]

[1]Laboratory of Organic Chemistry, ETH Zurich, Switzerland
[2]Department of Biochemistry, University of Zurich, Switzerland

Understanding of enzyme structure and function has come to a point where simple catalytic functions can be robustly designed into inert scaffolds on a routine basis [1]. Directed evolution can then be used to optimize the engineered activity to produce unnatural enzymes with enhanced characteristics. However, the ability to create increasingly efficient and sophisticated enzymes by computational design and directed evolution is limited by current understanding of engineered enzyme structure and how it relates to designed function. We are evolving a computationally designed enzyme that catalyzes the Kemp elimination, a simple model reaction for proton abstraction from carbon [2]. We have obtained high resolution X-ray crystal structures of both the apoenzyme, and the enzyme in complex with a transition state mimic. The structures have provided insight into the evolved catalytic mechanism, and have given feedback to focus further directed evolution and redesign efforts.

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Organic Chemistry **448**

Incorporation of *O*-Propargyl-tyrosine into Diketopiperazines by an Engineered Non-Ribosomal Peptide Synthetase

Hajo Kries[1], Rudolf Wachtel[2], Anja Pabst[3], Benedikt Wanner[1], Donald Hilvert[1]

[1]ETH Zürich, CH-8093 Zürich, [2]TU München, D-85747 Garching, [3]Universität Zürich, CH-8057 Zürich

In a continuous struggle with pathogens and competitors, many microorganisms have developed an arsenal of secondary metabolites for defense, among them nonribosomal peptides like penicillin. Since many of these secondary metabolites can be successfully repurposed as drugs, reliable methods for their combinatorial diversification and optimization for medical applications are desirable. Biological approaches to tailor the properties of nonribosomal peptides benefit from the modular architecture of the nonribosomal peptide synthetases (NRPSs) responsible for their biosynthesis. We set out to explore the substrate scope of NRPS modules by introducing single mutations at the substrate recognition site of an adenylation domain (PheA) governing substrate selectivity in the first module of the gramicidin S synthetase. PheA was mutated and then screened for promiscuous activities in a plate-based enzymatic assay. A tryptophan to serine mutation switched the substrate selectivity from phenylalanine to tyrosine. Further characterization revealed an even higher selectivity for *O*-propargyl-tyrosine and other phenylalanine derivatives with large substituents at the para-position of the phenyl ring. Reintroduced into a two module domain excised from tyrocidine synthetase, this single mutation enabled enzymatic synthesis of a cyclic dipeptide (diketopiperazine) from *O*-propargyl-tyrosine and proline even in the presence of competing phenylalanine. Diketopiperazines often show biological activities themselves. More importantly, the same type of phenylalanine activating module investigated here is found in a broad range of NRPSs. Consequently, our approach for substituting phenylalanine with *O*-propargyl-tyrosine should be generally applicable to the production of nonribosomal peptides that can be easily modified by click chemistry.

Organic Chemistry **449**

Asymmetric Michael Reactions Catalyzed by an Artificial Retro-Aldolase Enzyme

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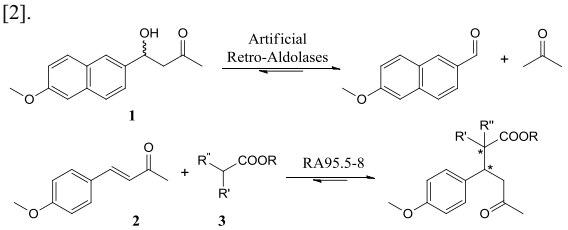
Laboratory of Organic Chemistry, ETH Zurich, 8093 Zurich, Switzerland

Innovative approaches to the computational de novo design of proteins are affording artificial enzymes with unprecedented activities. Recently, our group participated in the creation of protein scaffolds with incipient retro-aldolase activity [1], which were substantially improved by directed evolution [2].



We are exploring the catalytic promiscuity of RA95.5-8, an outstandingly active retro-aldolase, towards alternative amine-mediated reactions. RA95.5-8 catalyzes the asymmetric Michael reaction of **2** and activated esters (**3**) with comparable kinetics to the retro-aldol cleavage of **1**, which guided the design and evolution of the enzyme. The reaction mechanism, stereochemical outcome, and substrate scope of these enzymatic conjugate additions are currently under study in our lab.

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Organic Chemistry **450**

NIR Imaging Probe for Atherosclerosis with MMP2-Specific Ligand Site

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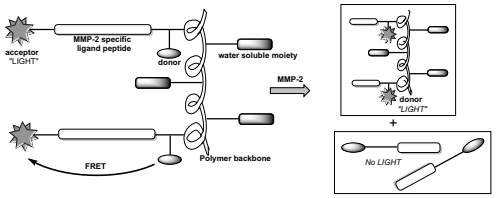
To date, atherosclerosis remains one of the most elusive symptoms to be accurately detected and non-invasively diagnosed. Several probes for *in vivo* detection of matrix metalloproteinase (MMP) family have been previously reported[1][2]. However, none of them allows quantification of atherosclerosis progression. To overcome this limitation, we focus on the development of NIR-imaging agents targeting MMP2, which is overexpressed in atherosclerosis using ligands with high binding and selectivity for MMP2.



Shown above is the outline of the molecular design of a NIR imaging probe for atherosclerosis detection with MMP2-specific peptide ligands. Based on the current literature [3], we have chosen a peptide sequence to serve as our prototype sequence of our first generation NIR imaging agent due to its high selectivity and binding potency at MMP2 compared to MMP9 and other MMPs.

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Organic Chemistry **451**

1,3-dipolar cycloaddition to C_{60} and TNT-EMF

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The discovery of Trimetallic Nitride Template Endohedral MetalloFullerenes (TNT-EMF) by Dorn and co-workers [1] provided a new class of metallofullerenes with a wide range of applications such as solar cells and MRI contrast agent [2]. Derivatization and functionalization of TNT-EMF attract a high interest [3].

In this study we investigated 1,3-dipolar cycloaddition reaction to C_{60} and $M_3N@C_{80}$ (M = Sc, Lu, Y, Gd) to compare their reactivity and regioselectivity. While only [6,6]-adduct was obtained in the reaction of C_{60}, both [5,6]- and [6,6]-adducts were provided in $M_3N@C_{80}$ with reactivity of Gd > Y > Lu > Sc (from higher to lower).

C_{60} $M_3N@C_{80}$

Our present effort is to develop a metallofullerene material with a water soluble anchors for MRI-applications.

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Organic Chemistry **452**

Tröger's base analogues: Methodology and Catalysis

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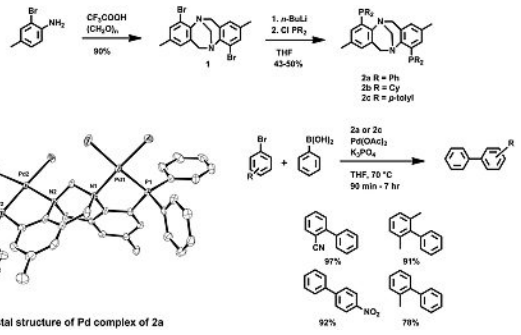
Department of Chemistry and Applied Biosciences, ETH Zurich, Wolfgang-Pauli-Str. 10, 8093 Zurich, Switzerland

Tröger's base[1] and its analogues are usually viewed as chiral molecules possessing stable stereogenic nitrogen atoms. Reports pertaining to their use in catalysis are limited.[2] We explore the Tröger's base scaffold as a potential motif for bulky tertiary phosphines. Here we report the synthesis, characterization and catalytic potential (Suzuki coupling) of novel P,N-ligands based on Tröger's base.



Crystal structure of Pd complex of 2a

These first generation phosphines with their modest catalytic activity motivated us to carry out further research. Our current efforts are concentrated on permutation of the position of the phosphine on the Tröger's base scaffold.

[1] J. Tröger, *J. Prakt. Chem.* **1887**, *36*, 225-245.
[2] S. Sergeyev, *Helv. Chim. Acta* **2009**, *92*, 415-444.

Organic Chemistry **453**

Abietane Diterpenoids from *Salvia sahendica* - Antiprotozoal Activity and Determination of Their Absolute Configurations

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[1] Division of Pharmaceutical Biology, University of Basel 4056 Basel
[2] Medicinal Plants and Drugs Research Institute, Shahid Beheshti University, G. C., Tehran, Iran
3 Department of Medical Parasitology and Infection Biology, Swiss Tropical and Public Health Institute and University of Basel, 4003 Basel
[4] Division of Molecular Modeling, University of Basel, 4056 Basel

In a screening of Iranian plants for antiprotozoal activity, a n-hexane extract of roots of *Salvia sahendica* potently inhibited the growth of *Plasmodium falciparum* K1 strain. Subsequent HPLC-based activity profiling led to identification of seven known and one new abietane-type diterpenoids. Structure elucidation was achieved by analysis of spectroscopic data including 1D and 2D NMR. The absolute configuration of sahendol and sahandone were assigned by comparison of experimental CD spectra with calculated ECD data, using time dependence density function theory (TDDFT) and methanol as solvent (B3LYP-SCRF /6-31G**).

In vitro biological activity against *Plasmodium falciparum* and *Trypanosoma brucei rhodesiense* STIB 900 strain, and cytotoxicity in rat myoblast (L6) cells were determined. The IC_{50} values of the compounds ranged from 0.85 µM to over 8.79 µM against *P. falciparum,* and from 1.79 µM to over 32.3 µM against *T. brucei rhodesiense*. Selectivity indices were from 0.1 to 18.2.

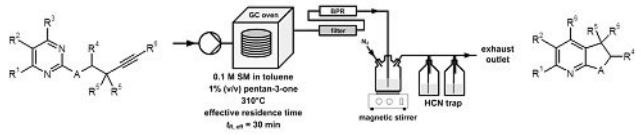
Organic Chemistry **454**

Flow Chemistry as a Useful Tool for the Modern Synthetic Chemist

Christoph Kuratli, Rainer E. Martin, Falk Morawitz, Mario Lenz

F. Hoffmann-La Roche AG, pRED, Pharma Research & Early Development, Small Molecule Research, Medicinal Chemistry, Grenzacherstrasse 124, Basel, Switzerland

Flow chemistry has attracted considerable attention over recent years as an enabling and innovative technology that significantly enhances the classical process window typically accessible with standard batch laboratory equipment. Unconventional and harsh reaction conditions such as greatly elevated temperatures and pressures can be generated easily allowing the superheating of organic solvents far beyond their boiling point in a controlled and safe manner. Furthermore, reactions which were formerly avoided due to serious safety concerns can now be conducted conveniently in flow as only small quantities of reactive materials or hazardous intermediates are within the reactor at a given time. Flow chemistry thus offers an ideal opportunity to revisit challenging, difficult to operate or dangerous reactions that have been underutilized in the past.[1] In addition, flow chemistry also allows for automation of operations thus speeding up the chemical synthesis process.
We will show some selected synthetic examples that illustrate the usefulness of flow chemistry for the preparation of pharmaceutically relevant structures.



[1] R. E. Martin, F. Morawitz, C. Kuratli, A. M. Alker, A. I. Alanine, *Eur. J. Org. Chem.* **2012**, *54*, 47-52.

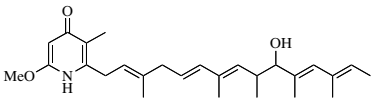
Organic Chemistry **455**

Towards the Total Synthesis of JBIR-02 and Related Piericidins

Johannes Hoecker, Gregor Meier and Karl Gademann*

University of Basel, St. Johanns-Ring 19, 4056 Basel, Switzerland.

Piericidins – structural homologs to ubiquinones (coenzyme Q) – are known for their very potent inhibition of Complex I (NADH:ubiquinone oxidoreductase) of the mitochondrial electron transport chain (K_i = 0.6 – 1.0 nM). In our program of modifying natural scaffolds to obtain biological tools to understand their mode of action and use this knowledge to enhance their therapeutic potential,[1] the pyridone JBIR-02[2], which showed promising anticancer properties was chosen as a starting point.



JBIR-02

In this context, we report our versatile synthetic strategy in the total synthesis of this target and related natural piericidins.

[1] S. Bonazzi, O. Eidam, S. Güttinger, J.-Y. Wach, I. Zemp, U. Kutay, K. Gademann, *J. Am. Chem. Soc.* **2010**, *132*, 1432-442; J.-Y. Wach, S. Güttinger, U. Kutay, K. Gademann, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2843-2846; J.-Y. Wach, K. Gademann, *Synlett* **2012**, *23*, 163-170.
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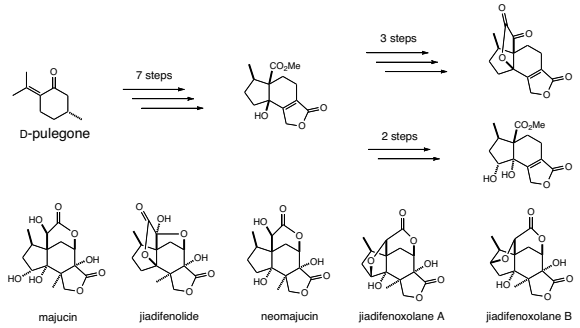
Organic Chemistry **456**

A Unified Approach Towards the Total Synthesis of Majucin-Type *seco*-Prezizaanes

José Gomes, Elias Kaufmann, Christophe Daeppen, and Karl Gademann*

University of Basel, St. Johanns-Ring 19, 4056 Basel, Switzerland

The progression of Alzheimer's, Parkinson's, and Huntington's disease have been linked to decreased neurotrophic support. Therefore, neurotrophins have been selected as candidates for a successful therapeutic strategy aimed at controlling these medicinal challenges.[1] An attractive approach is based on the search for orally bioavailable small organic molecules that could mimic or enhance neurotrophin (e.g. *nerve growth factor*) action.



In search for such compounds, some majucin-type *seco*-prezizaanes, found in the pericarps of *Illicium majus*, have shown to exhibit neurotrophic activity at very low concentrations.[2] We will present our results towards the total synthesis of majucin-type *seco*-prezizaanes.

[1] J. Corcoran, M. Maden, *Nat. Neurosci.* **1999**, *2*, 307.
[2] Y. Fukuyama, J.-M. Huang, *Studies in Natural Products Chemistry*, Elsevier **2005** Vol. 32.

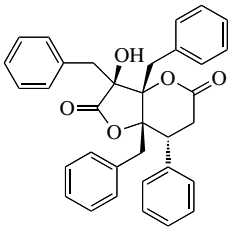
Organic Chemistry **457**

Towards the Synthesis of Ophiodilactones A and B

Samuel Bader, Jean-Yves Wach, Michael Lüscher, Karl Gademann*

University of Basel, Department of Chemistry, St. Johanns-Ring 19, CH-4056 Basel, Switzerland

Recently, Matsunaga *et al*. isolated the tetrameric phenylpropanoids ophiodilactones A (**1**) and B (**2**) from the starfish *Ophiocoma scolopendrina*. Both compounds showed moderate cytotoxic activity against P388 murine leukemia cell lines [1]. The γ,δ-dilactonic core structure is uncommen in nature and synthetic examples are rare in literature [2][3]. The intriguing architecture combined with the biological activity of ophiodilactone A and B aroused our interest and let us start a program directed towards their total synthesis.



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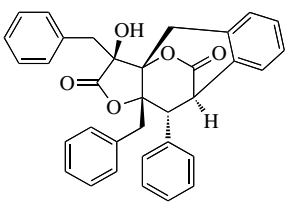

2

Key challenges of the synthesis are the four contiguous stereogenic centers, the dilactone moiety, and the unusual α-arylated lactone in compound **2**. We will present our achievements towards the total synthesis of the ophiodilactones A and B.

[1] R. Ueoka, T. Fujita, S. Matsunaga, *J. Org. Chem.* **2009**, *74*, 4396.
[2] W. Borsche, *Chem. Ber.* **1916**, *49/II*, 2538.
[3] T. Kapferer, R. Brückner, *Eur. J. Org. Chem.* **2006**, *9*, 2119.

Organic Chemistry **458**

Neuritogenic Pyridone Alkaloids: an SAR Study

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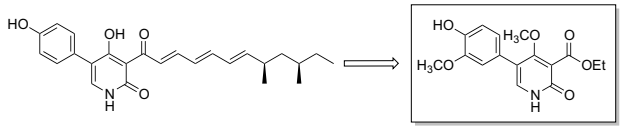
[1] University of Basel, Department of Chemistry, St. Johanns-Ring 19, 4056 Basel, Switzerland
[2] University of Zürich, Institute of Organic Chemistry, Winterthurerstrasse 190, 8057 Zürich, Switzerland

Increasing life expectancy in industrialized regions is accompanied by a higher incidence of neurodegenerative diseases such as Alzheimer's or Parkinson's disease. The treatment of such diseases, as well as the reconstruction of damaged nervous tissue in general (e.g. after spinal cord injuries) is either cumbersome or not possible today. Small organic molecules might provide a valuable approach towards this task.[1]



Natural product hit structure — Optimised synthetic lead compound

As a part of our total synthesis program on neuritogenic pyridone alkaloids,[2] we were intrigued to further investigate the relationship between their molecular structure and biological activity. Here, we present the results of an SAR study wherein we were able to encircle the neuritogenic core structure, reduce molecular complexity and increase biological activity in a reductionist approach.

[1] For reviews see: a) D. M. Skovronsky, V. M.-Y. Lee, J. Q. Trojanowski, *Annu. Rev. Pathol. Mech. Dis.*, **2006**, *1*, 151; b) D. Dawbarn, S. J. Allen, *Neuropath. App. Neuro.* **2003**, *29*, 211; c) R. M. Wilson, S. J. Danishefsky, *Acc. Chem. Res*, **2006**, *39*, 539.
[2] H. J. Jessen, A. Schumacher, T. Shaw, A. Pfaltz, K. Gademann, *Angew. Chem. Int. Ed.* **2011**, *50*, 4222; H. J. Jessen, A. Schumacher, F. Schmid, A. Pfaltz, K. Gademann, *Org. Lett.* **2011**, *13*, 4368.

Organic Chemistry **459**

Total Synthesis of Gelsemiol and Studies Towards Glycosylated Natural Congeners

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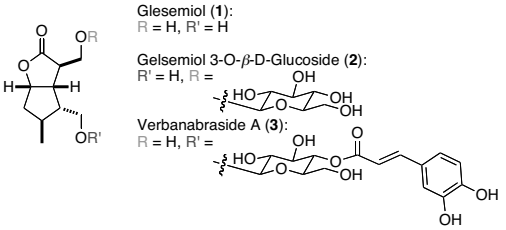
University of Basel, Department of Chemistry, St. Johanns-Ring 19
CH-4056 Basel, Switzerland

In an aging society, certain neurodegenerative diseases such as Alzheimer's or Parkinson's become more and more accentuated. Today's treatments are mainly symptomatic and do not address the regeneration of damaged neuronal networks. Therefore, our research is focused on the stimulation of neurite outgrowth applying natural products and their derivatives, capable of mimicking neurotrophic factors.[1]

Gelsemiol is known to induce neutrite outgrowth in the PC-12 cell line.[2] The enantioselective total synthesis of gelsemiol (**1**) is presented in nine steps with an overall yield of 14%. Chemical studies towards its congeners **2**, **3**[3] and biological evaluation in multiple cell models will be discussed.



[1] DeKosky, S. T.; Scheff, S. W. *Ann. Neurol.* **1990**, *27*, 457.
[2] Jensen, S. R.; Krik, O.; Norrestam, R.; *Phytochem.* **1987**, *26*, 2735.
[3] Ono, M.; Oishi, K.; Abe, H.; Nohora, T.; *Chem. Pharm. Bull.* **2006**, *54*, 1421.

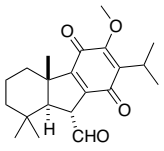
Organic Chemistry **460**

Total Synthesis of Taiwaniaquinone F Based on a Biogenetic Hypothesis

Christophe Thommen, Chandan Kumar Jana and Karl Gademann

Universität Basel, St. Johanns-Ring 19, 4056 Basel, Switzerland

Taiwaniaquinoids are natural rearranged diterpenoids that were first isolated from *Taiwania cryptomerioides*.[1] Taiwaniaquinones F and H possess interesting biological activities such as potent cytotoxicity against epidermoid carcinoma.[2] The uncommon 6-5-6 tricylic structure of these rearranged diterpenes led us to formulate a hypothesis concerning their biogenesis based on a *benzilic acid* type rearrangement for the key ring contraction.[3]



taiwaniaquinone F

Herein, we provide further experimental support for this hypothesis by demonstrating that also C_{20} taiwanaiquinoids such as the title compound can be accessed. Synthetic taiwaniaquinone F was obtained by a concise, protecting group free approach. Consequences for the biogenesis of related congeners will be discussed.

[1] (a) Lin, W. H.; Fang, J. M.; Cheng, Y. S. *Phytochemistry* **1995**, *40*, 871–873; (b) Lin, W. H.; Fang, J. M.; Cheng, Y. S. *Phytochemistry* **1996**, *42*, 1657–1663.
[2] Chang, C. I.; Chang, J. Y.; Kuo, C. C.; Pan, W. Y.; Kuo, Y. H. *Planta Med.* **2005**, *71*, 72–76.
[3] (a) Jana, C. K.; Scopelliti, R.; Gademann, K. *Synthesis* **2010**, *13*, 2223–2232; (b) Jana, C. K.; Scopelliti, R.; Gademann, K. *Chem. Eur. J.* **2010**, *16*, 7692–7695.

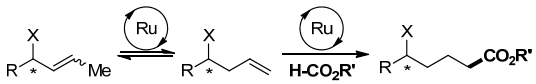
Organic Chemistry **461**

Auto-Tandem Catalysis with Ruthenium: Remote Hydroesterification of Olefins

Nicolas Armanino[1], Erick M. Carreira*[1]

[1] Laboratorium für Organische Chemie, ETH Zürich, CH-8093 Zürich, Switzerland.

One-pot processes that involve cascading reactions provide attractive tools for organic synthesis by simplifying operations and reducing the number of required intermediate isolations. Of particular interest are reactions that use a single catalytic entity capable of promoting multiple distinct steps without the need for operator intervention. In the course of our investigations, we have developed an auto-tandem catalytic system for the isomerization-hydroesterification sequence of internal olefins.



The system is based on low-valent ruthenium carbonyl clusters, enabling the incorporation of a C_1-unit by C-C bond formation onto a broad scope of allylic amines and alcohols. The process is characterized by operational simplicity, results in the functionalization of a remote position of the substrate and permits easy access to chiral lactone and lactam building blocks. Our mechanistic working model suggests that the key to success in this cascade is the formation of an active ruthenium cluster hydride by metal protonation, capable of promoting fast olefin isomerization that prevails over undesired decarbonylation pathways.

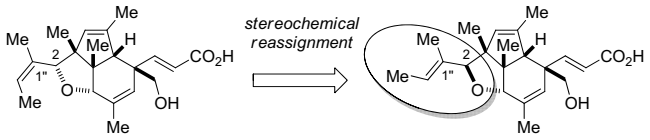
Organic Chemistry **462**

Total Synthesis and Stereochemical Reassignment of (±)-Indoxamycin B

Oliver F. Jeker, Erick M. Carreira*

Laboratorium für Organische Chemie, ETH Zürich, Wolfgang-Pauli-Strasse 10, CH-8093 Zürich, Switzerland

The indoxamycins are a novel class of six antitumor antibiotics that were isolated in 2009 form saline cultures of marine-derived actinomycetes [1]. Their highly congested carbon skeleton, in conjunction with the biological activity, renders these unusual polyketides notable as targets for synthetic studies.



The first total synthesis of (±)-indoxamycin B culminates in the stereochemical reassignment of the natural product [2]. The synthetic route relies on an efficient carboannulation sequence to rapidly access a key dihydroindenone intermediate. Moreover, a series of modern metal-catalyzed transformations allows for the construction of the tricyclic core framework.

[1] a) S. Sato, F. Iwata, T. Mukai, S. Yamada, J. Takeo, A. Abe, H. Kawehara, *J. Org. Chem.* **2009**, *74*, 5502–5509; b) S. Sato, F. Iwata, T. Mukai, S. Yamada, J. Takeo, A. Abe, H. Kawahara, (Nippon Suisan Kaisha, Ltd.), WO 113725, **2010**.
[2] O. F. Jeker, E. M. Carreira, *Angew. Chem. Int. Ed.* **2012**, *51*, 3474–3477.

Organic Chemistry **463**

Synthetic Studies To A Collection of Isoprostanes Associated With Infectious And Inflammatory Disease

Julian Egger, Erick M. Carreira*

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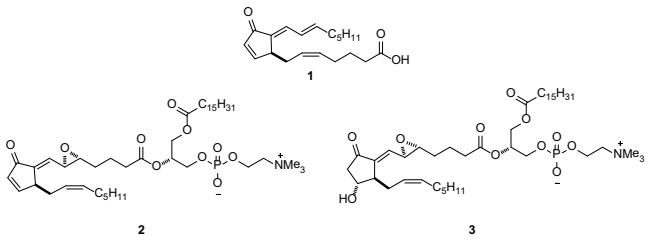
Though it is well established that prostaglandins and structural related isoprostanes feature a variety of biological activities, by far not all aspects of their physiological effects and molecular mechanisms are known [1]. Recent results show that our target molecules **1-3**, seem to play a pivotal role in inflammation processes associated with diseases like atherosclerosis or rheumatoid arthritis [2].



We have implemented novel tactics including some highly selective transformations into innovative synthetic routes to access these synthetically challenging molecules **1-3** in an efficient manner and thereby provide pure synthetic material that will allow further biological studies.

[1] J. U. Scher, M. H. Pillinger, *Clinical Immunology* **2005**, *114*, 100.
[2] U. Jahn, J.-M. Gallano, T. Durand, *Angew. Chem. Int. Ed.* **2008**, *47*, 5894.

Organic Chemistry **464**

Redoxactive Push-Pull Chromophores Based on Dialkynylazulene

Michael Koch, Olivier Blacque and Koushik Venkatesan

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During recent years push-pull chromophores have been extensively studied owing to their promising optoelectronic properties,[1] especially second- and third-order optical nonlinearities (NLO).[2] A typical organic push-pull chromophore consists of an electron acceptor and a donor bridged by a π-conjugated spacer. This arrangement facilitates efficient intramolecular charge-transfer and enables further tuning of the polarisability of the chromophore. Additionally, a planar structure ensures to retaining the π-conjugation over the entire donor-spacer-acceptor system.[4] Azulene possess a reversible redox behaviour and is as well a chromophore due to the inherent donor-acceptor property. A small donor-acceptor molecule with a small HOMO-LUMO gap like azulene is expected to have a tremendous advantage as a core structure for optoelectronic materials and could function as an valuable alternative to other organic structures and could aid in the development of new metal-free conducting materials. An in dept study of the azulene system with different disubstitution patterns regarding fluorescence as well as conducting properties has not been done until now. Since the electron distribution is very different at different positions of the azulene moiety the compounds show distinct properties. Based on their facile synthesis and their interesting emission properties, azulenes are interesting candidates for organic optoelectronic materials.[6] The fact that azulene is a redoxactive chromophore also makes it a promising candidate as core structure for photoswitching conducting systems.

[1] Ito, S.; Morita, N. Eur. *J. Org. Chem.* **2009**, 4567.
[2] Pasini, D.; Righetti, P. P.; Rossi, V. *Org. Lett.* **2002**, *4*, 23.
[3] Kival, M.; Diederich, F. Acc. Chem. Res. **2009**, *42*, 235.
[4] Yu, Y.-Y.; Fu, Y.; Lei, L.; Guo, Q.-X. *Chin. J. Chem.*, **2007**, *25*, 1041.
[5] Koch, M.; Blacque, O.; Venkatesan, K. *Org. Lett.*, **2012**, *14*, 1580.

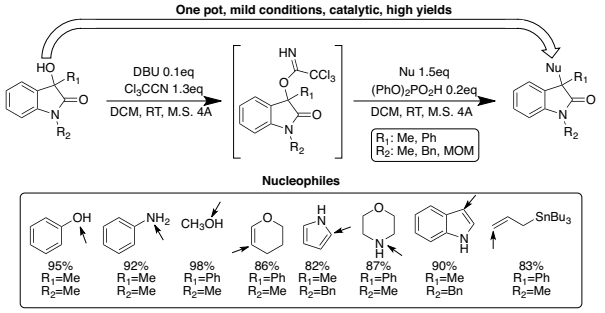
Organic Chemistry **465**

Construction of All Carbon Quaternary Centre: An Efficient Trichloroacetonitrile-assisted Nucleophilic Substitution on 3-Hydroxyindolin-2-one

Cyril Piemontesi[1], Qian Wang[1], Jieping Zhu[1]

[1]Ecole Polytechnique Fédérale de Lausanne, SB-ISIC-LSPN CH-1015 Lausanne, Switzerland

The construction of all-carbon quaternary center remains a challenging problem in organic chemistry, especially at the 3-position of oxindoles.[1] Recently, our group reported a new methodology to access 3-hydroxyindolin-2-ones and their transformation into spirooxindoles in a single step.[2] The present work reports the access to 3,3-disubstituted oxindoles directly from 3-hydroxyindolin-2-one in a one-pot stepwise sequence by using first a catalytic amount of DBU and trichloroacetonitrile followed by a catalytic amount of diphenylphosphoric acid and various nucleophiles. In this methodology, different nucleophiles were tested, providing 3,3-disubstituted oxindoles in good to excellent yields via the formation of C-C, C-O or C-N bonds.



[1] Zhou, F.; Liu, Y.-L.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381-1407.
[2] Gorokhovik, I.; Neuville, L.; Zhu, J. *Org. Lett.* **2011**, *13*, 5536-5539.

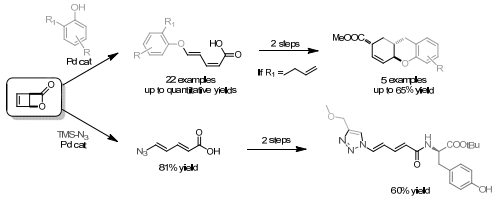
Organic Chemistry **466**

An Atom-Economical and Stereoselective Domino Synthesis of Functionalised Dienes

Caroline Souris, Davide Audisio and Nuno Maulide*

Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, 45470 Mülheim (Germany)

The electrocyclic ring-opening of cyclobutenes is a powerful, yet underutilised tool for the synthesis of diene building blocks [1]. We have developed an atom-economical synthesis of functionalised, stereodefined dienes that hinges on a novel domino allylic alkylation/electrocyclic ring-opening[2] sequence and allows direct access to doubly vinylogous esters and azidodienoic acids bearing challenging substitution patterns (Scheme 1).



Scheme 1. Domino allylic alkylation/4π electrocyclic ring opening using O- and N-nucloephiles and its applications

In this communication, a detailed overview of the scope and limitations of this transformation, as well as applications of the products obtained to target-oriented synthesis and chemical biology will be presented (Scheme 1).

[1] a) R. B. Woodward, R. Hoffmann, *Angew. Chem. Int. Ed.* **1969**, *8*, 781.; b) T. Durst, L. Breau, *Comprehensive Organic Synthesis*, Trost B. M., Flemming I., Paquette L. A., Eds Pergamon Press: Oxford 1991; Vol 5, chapter 6.1 pp 665-697

[2] C. Souris, M. Luparia, F. Frébault, D. Audisio, C. Farès, N. Maulide, *Submitted*.

Organic Chemistry **467**

Catalytic Asymmetric Diastereodivergent Deracemization

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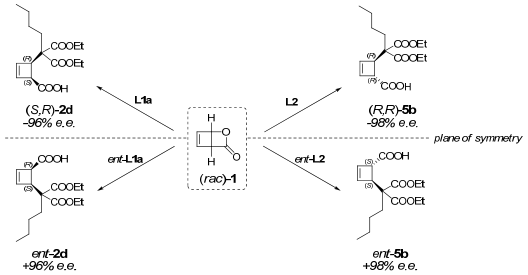
Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, 45470 Mülheim an der Ruhr, Germany

Deracemization is an important strategy through which a racemate can be converted into a 100% theoretical yield of a single enantiopure product. [1] Our group has developed a palladium-catalysed highly diastereoselective synthesis of functionalized *cis*-cyclobutenes starting from lactone **1**. The intermediacy of a symmetric intermediate raised the exciting prospect of deracemization of **1**.[2]

We report herein an unusual ligand-controlled Diastereodivergent Deracemization. Thus, either *cis*- or *trans*-disubstituted cyclobutenes can be obtained at will in good yields and excellent selectivites, starting from racemic **1**.[3]



[1] J. Steinreiber, K. Faber, H. Griengl, *Chem. Eur. J.* **2008**, *14*, 8060.

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[3] M. Luparia, M. T. Oliveira, D. Audisio, F. Frébault, R. Goddard, N. Maulide, *Angew. Chem. Int. Ed.* **2011**, 12631.

Organic Chemistry **468**

Workflow driven cheminformatics: easy ways to help you choose your next synthesis strategy

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[1]Reed Elsevier Properties SA, Espace de l'Europe 3, 2000, Neuchâtel, Switzerland

[2]Elsevier Information System GmbH, Theodor-Heuss-Allee 108, 60486 Frankfurt am Main, Germany

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Organic Chemistry **469**

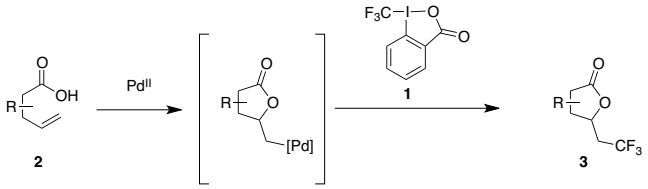
Tandem Pd(II) Catalyzed Oxycyclization and Trifluoromethylation Using a Hypervalent Iodine Reagent

Julie Charpentier, Antonio Togni*

Department of Chemistry and Applied Biosciences, Swiss Federal Institute of Technology, ETH Zürich, CH-8093 Zürich, Switzerland

Trifluoromethylated building-blocks are widely recognized as being very valuable in medicinal chemistry and drug-discovery. Synthetic methodologies include nucleophilic, radical and electrophilic trifluoromethylations. We have contributed to the latter approach with the development of hypervalent iodine (III) compounds, such as **1**, allowing the transfer of a formal "CF_3^+" group to various nucleophiles.[1]

Our current research includes the formation of $C(sp^3)$-CF_3 bonds to access lactones *via* a tandem palladium-catalyzed intramolecular addition of carboxylic acids to olefins and electrophilic trifluoromethylation.



[1] a) Eisenberger, P.; Gischig, S.; Togni, A. *Chem. Eur. J.* **2006**, *12*, 2579. b) Kieltsch, I.; Eisenberger, P.; Togni, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 754. c) Koller, R.; Stanek, K.; Stolz, D.; Aardom, R.; Niedermann, K.; Togni, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 4332. d) Niedermann, K.; Früh, N.; Vinogradova, E.; Wiehn, M.S.; Moreno, A.; Togni, A. *Angew. Chem. Int. Ed.* **2011**, *50*, 1059.

Organic Chemistry **470**

Access to Quaternary α-Trifluoromethylated Lactones

Václav Matoušek, Julie Charpentier, Raffael Koller and Antonio Togni

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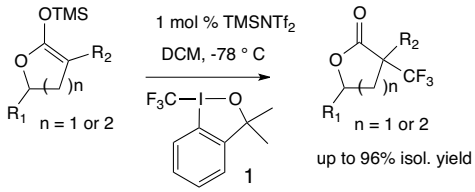

A range of five- and six-membered lactones were transformed into their corresponding trimethylsilyl ketene acetals which could be efficiently α-trifluoromethylated using hypervalent CF_3-iodine reagent **1** in the presence of catalytic amounts of $TMSNTf_2$ - a Lewis acid of remarkable oxophilicity. The presented mild transformation opens access to quaternary α-trifluoromethylated carbonyl compounds which are otherwise difficult to synthetize.

Based on our experimental observations, we assume that triflurometylation of trimethylsilyl ketene acetals proceeds through the intermediacy of activated O-silylated hypervalent iodine reagent **1** with a more pronounced iodonium character.

The scope of these transformations and a plausible reaction mechanism will be discussed.

Organic Chemistry **471**

Direct Electrophilic *N*-Trifluoromethylation of Azoles

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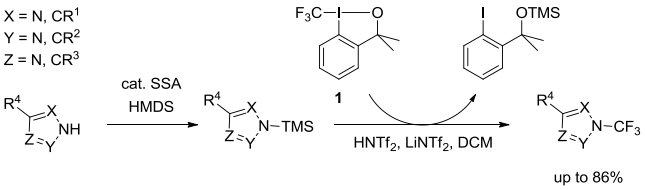
Due to its unique physiological properties,[1] the trifluoromethyl group has become over the last decade a privileged structural motive in drug development.

We recently reported the direct electrophilic *N*-trifluoromethylaton of a variety of nitrogen containing heterocycles, such as tetrazoles, triazoles, indazoles and pyrazoles[2] using the hypervalent iodine reagent **1**, originally developed in our group.[3]

After *in situ* trimethylsilylation, the heterocyclic substrates were converted under acidic conditions to the *N*-trifluoromethylated species in good to excellent yields.



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Organic Chemistry **472**

Reductive Eliminations from λ^3-Iodanes: Understanding Selectivity and the Crucial Role of the Hypervalent Bond

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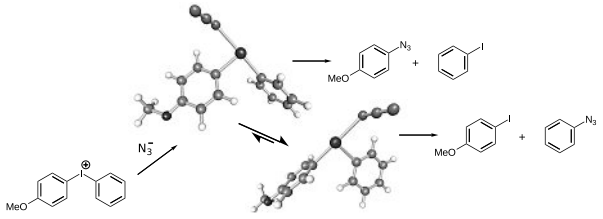
ETH Zürich, Wolfgang-Pauli-Strasse 10, CH-8093 Zürich, Switzerland

λ^3-iodanes were shown to be powerful agents for the selective functionalization of arenes[1]. The present computational study is focused on the investigation of the properties which govern the selectivity of the reductive elimination of arene groups in iodanes. It was shown that diaryliodoniums are the precursor compounds, which form a reactive λ^3-iodane with a nucleophile establishing a 3-center-4-electron bond. The result is an intermediate equilibrium between two iodane isomers. From each of the two isomers a reductive elimination is possible, leading to two different products. The two isomers are in rapid equilibrium (Curtin-Hammett) such that each reductive elimination step is rate-determining. Furthermore, the selectivity of the reductive elimination correlates with the polarity of the hypervalent bond.



[1] B. Wang, J. W. Graskemper, L. Qin, S. G. Di-Magno, *Angew. Chem. Int. Ed.* **2010**, *49*, 4079.

Organic Chemistry **473**

Catalytic Formal [3+2] Annulations of Aminocyclopropanes for the Enantiospecific Synthesis of Five-Membered Rings.

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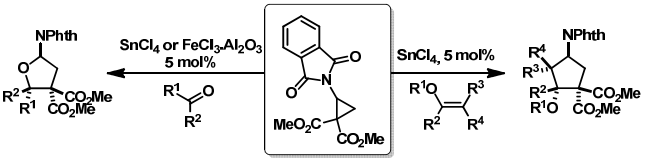
Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland

Donor-Acceptor cyclopropanes[1] are powerful and versatile building blocks for organic synthesis as they leads to a reactive formal 1,3 dipole intermediates.

When considering the importance of nitrogen-containing functional groups in drugs and natural products, it is surprising that donor-acceptor aminocyclopropanes[2] were never used in formal cycloaddition reactions. This is probably due to the formidable challenge associated with the synthesis and catalytic activation of these compounds, which have been used only as structural elements so far. Through Lewis-Acid activation, we report herein the first catalytic formal [3+2] annulations of aminocyclopropane with silyl enol ethers[3], aldehydes[4] and ketones[5].



Complete control over the diastereoselectivity of the reaction was achieved. The obtained aminocyclopentanes or aminotetrahydrofurans are useful building blocks and further functionalization gives easy access to scaffolds found in various bioactive compounds.

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Organic Chemistry **474**

The formal homo-Nazarov cyclization - a powerful tool for the synthesis of alkaloid natural products

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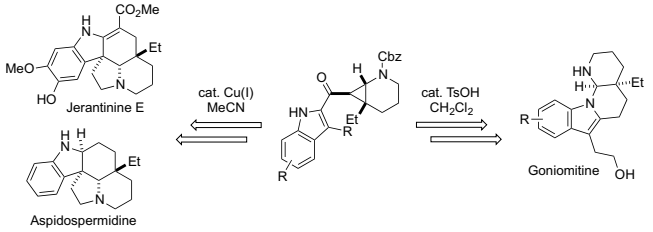
*Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland

Heterocyclic scaffolds occupy a privileged position among natural and synthetic drugs. Consequently, the discovery and implementation of cyclization reactions to efficiently access such cyclic structures are highly sought after in organic chemistry. In this context, our laboratory developed the first catalytic formal homo-Nazarov cyclization of vinyligous cyclopropyl ketones for the synthesis of polycyclic hetero and non-hetero cyclohexenone derivatives.[1] Herein we report application of the developed mild and highly regioselective reaction for the cyclization of acyl indole substituted aminocyclopropanes. The effectiveness of the methodology is demonstrated by the efficient formal total synthesis of aspidospermidine and the total synthesis of goniomitine.[1b] The generalizability of the method is further showcased by the first synthesis of the highly electron-rich, apidosperma type alkaloid jerantinine E.



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Organic Chemistry **475**

Pd-Catalyzed C-H Alkynylation of Heterocycles

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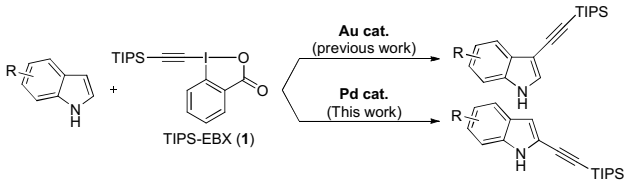
Heterocycles are omnipresent in organic and medicinal chemistry. In the context of sustainable chemistry, it is essential to develop direct C-H functionalization methods to generate new heterocyclic structures.[1] Whereas arylation and vinylation methods are already well developed, alkynylation has been much less investigated, despite the fact that acetylenes are one of the most useful building blocks in organic chemistry.

In our laboratory, we have introduced ethynyl benziodoxolone (EBX) reagents as electrophilic alkynylation reagents and used them in the gold-catalyzed functionalization of biologically important indole and pyrrole heterocycles.[2] In particular, the use of TIPS-EBX (**1**) gave excellent selectivity for the 3-alkynylation of indoles.

In this work, we report the use of Pd catalysis for an unprecedented C2-selective alkynylation, a process that has been realized only for 3-substituted indoles in the past.[3] In addition, the synthesis of new hypervalent iodine reagents and their use in the alkynylation reaction will also be presented.



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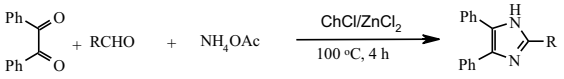
Organic Chemistry **476**

Green synthesis of trisubstituted imidazoles in deep eutectic solvent

Najmaddin Azizi, Amin Rahimzadeh Oskooee

Chemistry and Chemical Engineering Research Center of Iran. P.O. Box: 14335-186, e-mail:Aminiran1367@yahoo.com

Great efforts have been focused on synthesizing libraries of small heterocyclic molecules because of their high degree of structural diversity and extensive utility as therapeutic agents. Also, multi-component reactions are convergent reactions in which three or more starting materials react to form a product, where basically all or most of the atoms contribute to the newly formed molecule [1]. Undoutedlt, naturally occurring substituted imidazoles, as well as synthetic derivatives thereof, play an important role in chemical and biological systems [2]. Therefore, the development of a new catalytic system to overcome these shortcomings and fulfill the criteria of a mild, efficient and environmentally benign protocol for the synthesis of highly substituted imidazoles is an important task for organic chemists.
In this study the possibility of performing these organic transformations by using water as green solvent or under solvent-free conditions evaluated. Herein, we report, a simple and practical synthesis of trisubstituted imidazoles promoted by deep eutectic solvent under mild reaction conditions.



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[2] (a) Lambardino, J. G.; Wiseman, E. H. *J. Med. Chem.* **1974**, *17*, 1182-1188.; (b) Sundberg, R.; Martin, R. B. *Chem. Rev.* **1974**, *74*, 471-517 (c) M. R. Katritzky, A. R.; Rees, C.; Scriven E. F. V. In Comprehensive Heterocycle Chemistry II; Eds.; Pergamon Press: Elmsford, NY, 1996; Vol. 3, pp 77-220.

Organic Chemistry **477**

Ultrasound mediated synthesis of 1,3-oxathiolane-2-thiones in water

Amin Rahimzadeh oskooee

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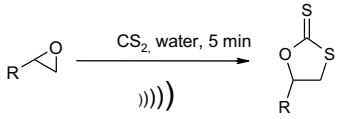
Organic dithiocarbamates are valuable synthetic intermediates which are ubiquitously found in the variety of biologically active compounds. Functionalization of the carbamate moiety offers an attractive method for the generation of derivatives, which may constitute interesting medicinal and biological properties. For these reasons, the synthesis of dithiocarbamate derivatives with different substitution patterns at the thiols chain has become a field of increasing interests in synthetic organic chemistry during the past few years [1,2].
Therefore, the syntheses of biologically important 1,3-oxathiolane-2-thiones have received considerable attention, and there are some reports for the synthesis of dithiocarbamate derivatives in the literature. However, there are various limitations such as long reaction times, use of organic solvents, high temperatures, moderate yields and limited substrate. Given the widespread availability of carbon disulfide and epoxides, there is substantial interest in developing efficient reaction from these simple starting materials. Herein, we report the extension of this methodology to the ultrasound promoted green synthesis of 1,3-oxathiolane-2-thiones in pure water with a view to explore the yields and rate of reaction.



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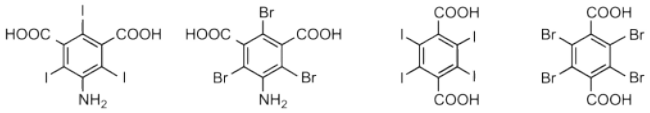
Organic Chemistry **478**

Halogenated ligands for the structure determination of proteins

Tobias Beck[1], Tim Grüne[2], George M. Sheldrick[2]

[1]ETH Zürich, Wolfgang-Pauli-Str. 10, 8093 Zürich, Switzerland
[2]Georg-August-Universität Göttingen, Tammannstr. 4, 37077 Göttingen, Germany

Obtaining phase information for the solution of macromolecular structures is still one of the major challenges in X-ray crystallography. A new class of halogenated ligands has been established for heavy-atom derivatization of biological macromolecules. I3C and B3C contain an easily recognizable arrangement of three anomalous scatterers (iodine or bromine, respectively) and three functional groups for hydrogen bonding to proteins.



I3C B3C I4C B4C

It was demonstrated that I3C is suitable for structure solution using single-wavelength anomalous dispersion [1,2]. The bromine derivative B3C, suitable for multi-wavelength anomalous dispersion experiments, was employed for experimental phase determination using synchrotron data [3]. Recently, I4C and B4C, each containing four halogen atoms, have been utilized for structure determination of several proteins. These compounds provide greater anomalous signal per molecule and possess different binding properties.

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[3] T. Beck, T. Gruene, G. M. Sheldrick, *Acta Crystallogr. Section D* **2010**, *66*, 374.

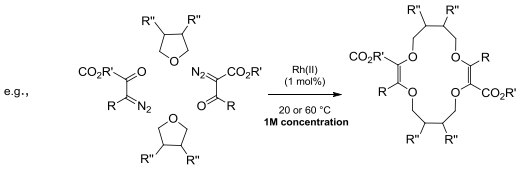
Organic Chemistry **479**

One-Step Synthesis of Functionalized Polyether Macrocycles

Mahesh Vishe[1], Radim Hrdina[1], Daniele Poggiali[1], Céline Besnard[2], Laure Guénée[2], Jérôme Lacour[1]*
[1]Department of Organic Chemistry and [2]Laboratory of Crystallography, University of Geneva, Quai Ernest Ansermet 30, CH-1211 Geneva

Macrocycles are generally synthesized from linear molecules using intramolecular reactions.[1] Recently our group has developed several one-step syntheses of medium sized rings[2] and polyether macrocycles by multi-condensation reactions of simple (naked) ether and diazo reactants under high concentration and non-templated conditions. [3]

Here in an extension of this research we present a series of Rh(II)-catalyzed[4] reactions of diazocarbonyls and substituted tetrahydrofuranes and tetrahydropyranes that afford 16- to 18-membered macrocycles in a single step and yields up to 84 %. A rather high functional group tolerance is exhibited. Mechanistic rationals for these macrocyclisation reactions will also be presented.



[1] H. An, J. S. Bradshaw, R. M. Izatt, *Chem. Rev.* **1992**, *92*, 543.
[2] R. Ballesteros-Garrido, D. Rix, C. Besnard, J. Lacour, *Chem. Eur. J.* **2012**, in press
[3] W. Zeghida, C. Besnard, J. Lacour, *Angew. Chem. Int. Ed.* **2010**, *49*, 7253.; D. Rix, R. Ballesteros Garrido, W. Zeghida, C. Besnard, J. Lacour, *Angew. Chem. Int. Ed.* **2011** , 50, 7308.

Organic Chemistry **480**

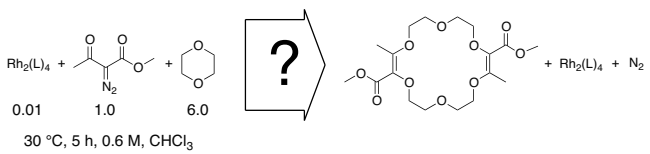
On the Mechanism of One-Step Multi-Component Macrocyclization Reactions

Daniele Poggiali, Diane Rix, Rafael Ballesteros-Garrido, Walid Zeghida, Jérôme Lacour[1]

[1] Department of Organic Chemistry, University of Geneva, Quai Ernest Ansermet 30, CH-1211 Geneva.

Recently it has been shown that functionalized polyether macrocycles can be obtained in a single step by the condensation of 4 components, and this under high concentration and no-template effect. [1, 2, 3]

Herein we present a mechanistic study of such a Rh(II)-catalyzed reaction of diazodicarbonyls and 1,4-dioxane that affords 18-membered macrocycles. Kinetic information was gathered trough NMR and FT-IR monitoring. Further information was obtained via trapping reactions of intermediates.



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[2] D. Rix, R. Ballesteros Garrido, W. Zeghida, C. Besnard, J. Lacour, *Angew. Chem. Int. Ed.* **2011** , *50*, 7308.
[3] R. Ballesteros Garrido, D. Rix, C. Besnard, J. Lacour, *Chem. Eur. J.* **2012**, DOI : 10.1002/chem.201103870.

Organic Chemistry **481**

Modular Synthesis, Orthogonal Functionalization and Properties of Novel Cationic [6]Helicenes

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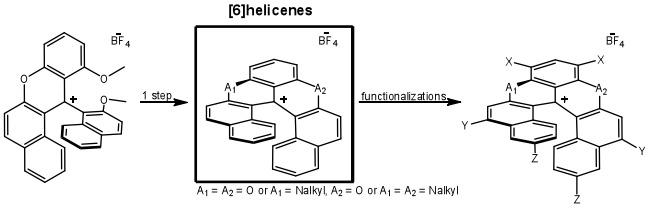
johann.bosson@unige.ch ; jerome.lacour@unige.ch

Helicenes are omnipresent in chemistry, biochemistry and physics as a result of their many different properties and applications [1]. These can be modulated by selectively introducing substituents to the periphery of the helical cores or by changing the nature of the atoms within. However, such modifications are not always trivial to perform. To overcome this limitation, we developed a new class of cationic diaza, azaoxo and dioxo [6]helicenes.



These derivatives were prepared in one step from a common advanced intermediate. Straightforward and orthogonal functionalizations afforded a series of polysubstituted [6]helicenes. The importance of these transformations was further evidenced in the strong modulation of the visible absorption properties of those cationic dyes.

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Organic Chemistry **482**

Carbenoid C-H Insertions into Tetrahydrofurans Catalyzed by CpRu Complexes

Cecilia Tortoreto, Thierry Achard and Jérôme Lacour*

Department of Organic Chemistry, University of Geneva
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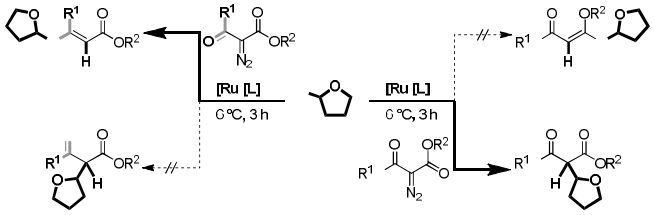
CpRu complexes are interesting alternatives to copper and dirhodium species for the catalyzed decomposition of diazo compounds [1]. Recently, our group has shown that combinations of $[CpRu(CH_3CN)_3][PF_6]$ and diimine ligands lead to O-H insertion and condensation reactions with nitriles, ketones and aldehydes [2]. Herein, in a new development, using α-diazo-β-ketoesters and THF moieties as substrates, we report the formation of novel enol-acetal motifs through unprecedented 1,3-C-H insertion reactions [3]. Interestingly, using malonates instead of β-ketoester diazo compounds, the same conditions provide the formation of the C-C bound adducts only. Mechanistic informations on this interesting dichotomy will be provided.



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Organic Chemistry **483**

Modular synthesis of pH-sensitive helical dyes

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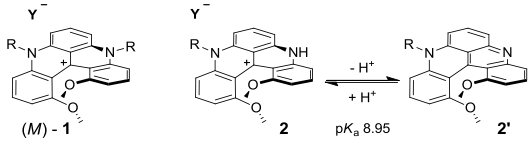
[1] University of Geneva, Quai Ernest Ansermet 30, CH-1211 Geneva.

Helicenes are *ortho*-condensed polyaromatic compounds which are chiral due to the helical conformation of their backbone.[1] Whereas hundreds of neutral helicenes can be found in the literature, only few cationic derivatives have been reported.[2] Previously, we have shown that cationic diaza[4]helicenes of type **1** can be readily prepared and resolved; these moieties displaying high barriers of racemization ($\Delta G^{\ddagger}$ 172.8 kJmol^{-1} at 200°C).[3,4]



Herein, we report the chemical (pH-sensitive, pK_a 8.95) and physical properties of novel quinacridine-based [4]helicenes **2**. We also report the extension of this chemistry to neutral dioxa-aza, diaza-oxa and triazatriangulenes.[3] Applications of such derivatives in synthetic chemistry will also be presented.

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Organic Chemistry **484**

Design, synthesis and application of a polymyxin B derivative suitable for photoaffinity labelling

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Polymyxin B is an antibiotic of last resort. It is active against gram-negative bacteria and displays a high binding affinity for lipid A, which is part of the bacterial lipopolysaccharide (LPS) and a major endotoxin. Unfortunately, polymyxin B has severe side effects, such as neurotoxicity and acute renal tubular necrosis. Therefore, understanding its mode of action is crucial to improve antibacterial activity. Membrane disruption, channel formation or mediation of contact between outer and inner membrane have been proposed as the major antibacterial effect. However, another mode of action has been proposed due to the following observations: pore formation effects have been reported at higher concentration than the minimal inhibitory concentration, and polymyxin B binds to the N-terminal domain of the prokaryotic Hsp90 to inhibit its chaperone activity. We report the efficient synthesis of polymyxin B3 and a derivative suitable for photoaffinity labelling using an orthogonal protecting group strategy on a solid support. The polymyxin B3 photoprobe contains a photoleucine and an alkyne-tag for detection using click chemistry. Preliminary photoaffinity labelling experiments will be presented.

Organic Chemistry **485**

Stereoselective Synthesis of a Bicyclic THP Peloruside A Analog and its Biological Evaluation

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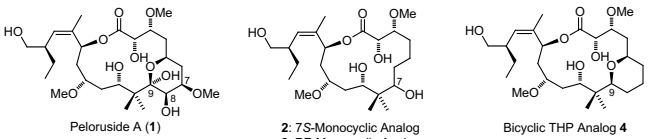
Peloruside A (**1**) is a marine natural product which was isolated in 2000 [1]. It was shown to exhibit potent taxol-like microtubule-stabilizing activity and to inhibit the growth of human cancer cell lines at nM concentrations [2]. The stereoselective synthesis of the two simplified monocyclic peloruside A analogs **2** and **3** have only recently been accomplished in our group [3]. In order to provide information on the importance of the substituents on the pyranose ring in natural peloruside A (**1**), the bicyclic THP analog **4**, which lacks the anomeric OH group at C9 as well as both oxygen substituents on C7 and C8, was targeted for synthesis.



In this contribution we will present the stereoselective synthesis of bicyclic THP analog **4** together with data on its effects on the tubulin/microtubule system and its *in vitro* antiproliferative activity, in comparison with monocyclic analogs **2** and **3**. Our synthesis of **4** is based on a high yielding *Prins* cyclization followed by macrolactonization of the corresponding *seco*-acid precursor.

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Organic Chemistry **486**

A modular system for the post-synthetic point-specific labeling of natural nucleic acids

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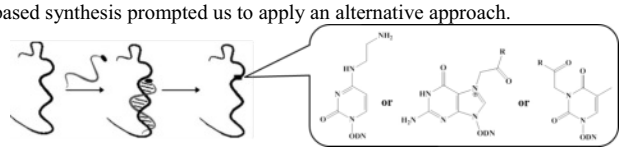
Non-natural modifications of oligonucleotides have unusual properties and can be used for a range of therapeutic and analytical purposes, including the regulation of gene expression, DNA-peptide interaction, as well as investigation of DNA and RNA tertiary structures [1]. Restriction of the lengths of such modified oligonucleotides accessible by automated phosphoramidite-based synthesis prompted us to apply an alternative approach.



The basic principles of this approach rely on the annealing of the *donor molecule* bearing a reactive group with the *target* oligonucleotide and on localizing the reactive group close in space to the target nucleotide [2]. The reactive group was designed in such a way that it can selectively modify a specific nucleotide (cytosine, guanine, or thymine) in the presence of the four others. The newly introduced group was efficiently used for labeling with a fluorophore, and hence the generation of a new bioorthogonal group was shown.

Financial support by the Swiss National Science Foundation (*SNSF-Professorship* PP002-119106/1 to EF) is gratefully acknowledged.

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Organic Chemistry **487**

The Standard Electrode Potential of 3-Nitrotyrosine

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Tyrosine and the associated tyrosyl radical are important one-electron transfer reactants in biology [1], and the according electrode potential at pH=7 has been determined by different methods [2]. 3-nitrotyrosine came to the attention of biologists and biochemists when its formation *in vivo* was detected [3]. The standard electrode potential of 3-nitrotyrosyl/3-nitrotyrosine has not been determined yet.

We used cyclic voltammetry to study the electrode reactions of *N*-acetyl-3-nitrotyrosine ethyl ester. Voltammograms at scan rates up to 250 V/s at a carbon microelectrode were recorded for pH values of 0.8, 3.8 and 7.4. All traces obtained show only anodic waves, the radicals produced by the oxidation disappear too fast to be detected in the cathodic scan. The peak potentials of the anodic currents do not depend on the scan rate, therefore the reaction must be reversible, and the equilibrium potential can be estimated from these waves alone. We applied the same method to tyrosine to obtain a reference value. Anodic peak potentials were independent of the scan rate, as before. The electrode potentials of both couples obey normal pH dependence with a slope of -59 mV per unit at room temperature. This corresponds to

$$Y^{\bullet} + e^{-} + H^{+} \rightleftharpoons YH$$

$E^{o\prime}$ at pH=7.4 for tyrosine was 0.95 V, for 3-nitrotyrosine it was 1.10 V, *vs.* NHE.

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Organic Chemistry **488**

New extended polycondensed aromatic hydrocarbon of the C60 class

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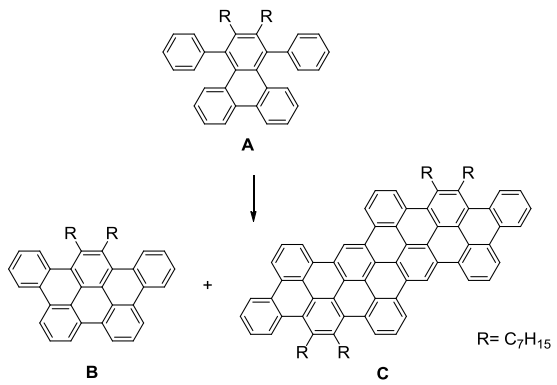
A classical Scholl oxidation of precursor A under Kowacic conditions ($FeCl_3/CH_3NO_2$ in CH_2Cl_2) yields predominantly and selectively the dimeric structure C instead of the expected tribenzopentaphene B, opening thereby a route to this strongly fluorescing C60 core structure, which displays a pronounced tendency for extended π-π stacking.



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Organic Chemistry **489**

Excess Electron Transfer in DNA Containing Multiple Phenanthrenes

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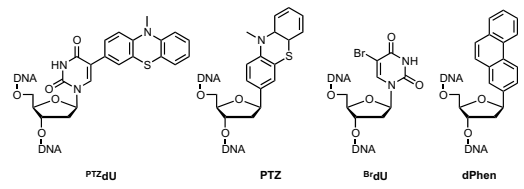
University of Bern, Departement of Chemistry and Biochemistry, Freiestrasse 3, CH-3012 Bern, Switzerland

In order to investigate excess electron transfer (EET) within a DNA duplex we synthesized oligonucleotides containing ^{PTZ}dU, PTZ, ^{Br}dU and dPhen. The hybridization properties of these duplexes were determined by UV melting curve analysis. The thermal melting temperatures revealed that PTZ, being a non-hydrogen bonding/intercalating base surrogate, is accommodated within the DNA duplex when paired against an abasic site. Selective photoexcitation of duplexes containing PTZ or ^{PTZ}dU initiated EET, which was quantified by polyacrylamide gel electrophoresis (PAGE). Preliminary results indicate that electron transfer through a DNA duplex containing three dPhen residues indeed occurs, suggesting interstrand stacking of the dPhen residues.



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Organic Chemistry **490**

Homo-DNA as a Reporting Unit for the Detection of Single Nucleotide Polymorphism

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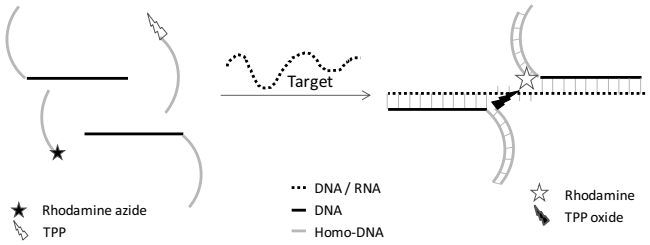
Although homo-DNA is composed of a six-membered ring sugar moiety it can form duplexes in an anti-parallel fashion with itself but not with natural nucleic acids. [1] For single nucleotide polymorphism (SNP) detection, both the sensing of the mismatch and the generation of a signal are necessary. In order to enhance sensitivity, templated chemistry can be employed. We showed previously that homo-DNA can be used as a template for the bioorthogonal Staudinger reduction of rhodamine azide by triphenylphosphine (TPP). [2] Here we show that chimeric oligonucleotides composed of an orthogonal homo-DNA and DNA domain, can successfully be applied for selective nucleic acid sensing, via homo-DNA templated fluorescence dequenching.



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Organic Chemistry **491**

Synthesis and Incorporation of Diazirine-Modified Uridine Phosphoramidite

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[1]Department of Chemistry and Biochemistry, University of Bern, Freiestrasse 3, 3012 Bern Switzerland

A diazirine-modified uracil analogue was synthesised and incorporated into three RNA 21-mers for use in detecting RNA –RNA binding protein (RBP) interactions.

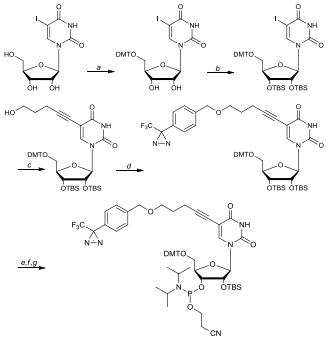

Figure 1. Synthesis of phosphoramidite **X**. *a)* DMTCl, DMAP, pyridine; *b)* TBSCl, DMF, 62% over 2 steps; *c)* 4-pentyn-1-ol, CuI, $Pd(PPh_3)_2Cl_2$, Et_3N, DMF, 71%; *d)* 3-(α-iodo-*p*-tolyl)-3-(trifluoromethyl)-3H-diazirine[1], NaH, THF, 51%; *e)* TBAF, THF, 73%; *f)* TBSCl, $AgNO_3$, pyridine, THF, 72%; *g)* CEPCl, DIPEA, THF, 75%.

Their crosslinking potential to single stranded binding proteins has been evaluated

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Organic Chemistry **492**

Synthesis of iso-bicyclo DNA

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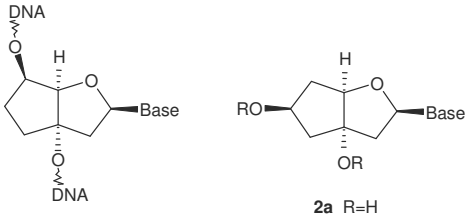
Freiestrasse 3, 3012 Bern, Switzerland

In the last two decades, a variety of modified nucleosides have been developed to improve antisense or siRNA oligonucleotide properties such as target affinity, nuclease resistance, and pharmacokinetics[1]. It is well established that conformational restriction leads to an enhancement in binding affinity and biostability due to an entropic advantage. In the context of conformational restriction our laboratory synthesized and characterized the analogue bicyclo-DNA **1**[2]. In continuation of this work we now envisaged the synthesis of 6'-hydroxy bicyclo nucleosides to investigate its structure-affinity relationship in complementary binding to DNA and RNA.

We present the synthesis of the building blocks A, C, G and T (**2a**), the incorporation into DNA and their pairing as well as their biological properties.



1 **2a** R=H **2b** R=DNA

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Organic Chemistry **493**

Palladium-Catalyzed Asymmetric α-Arylation of Aldehydes

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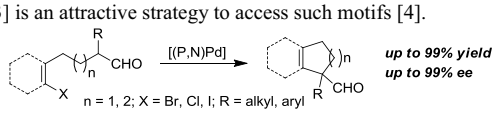
Our group has an interest in developing catalytic methods to access chiral aldehydes in view of further use in synthesis. In this context, we have recently developed an asymmetric isomerization of primary allylic alcohols [1] and an asymmetric hydroboration of terminal alkenes [2]. Although, high levels of enantioinduction were obtained for both reactions, none of these methods provides α-chiral aldehydes with a quaternary stereocenter. The underdeveloped Pd-catalyzed α-arylation of aldehydes pioneered by Miura [3] is an attractive strategy to access such motifs [4].



We will present the synthesis of an original class of chiral (P,N) ligands which, in combination with the proper palladium source, display unprecedented selectivity levels for the intra-molecular arylation of α-substituted aldehydes [5].

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Organic Chemistry **494**

Chiral *N*-Heterocyclic Carbenes in Asymmetric Gold Catalysis and in the Synthesis of NHC-borane complexes

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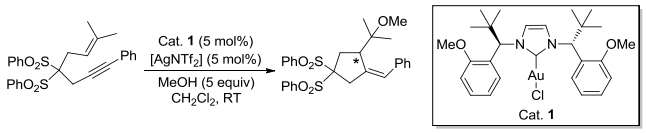
30 quai Ernest Ansermet, CH-1211 Geneva 4, Switzerland

We have reported a new family of chiral NHCs utilizing the concept of minimization of allylic strain to set the stereocontrol elements of the catalyst[1], which have been very successfully applied in the intramolecular arylation of amides to give 3,3-disubstituted chiral oxindoles[1] and in the first highly asymmetric Pd-catalyzed C–H coupling involving an unactivated methylene groups yielding highly enantioenriched fused indolines.[2]

In this contribution we report:

- Initial results of chiral NHC-gold catalyzed 1,6-enyne methoxycyclization reactions using the same ligands.



- Chiral NHC-borane complexes with a focus on synthesis and structural features.[3]

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[2] a) Nakanishi, M.; Katayev, D.; Besnard, C.; Kündig, E. P. *Angew. Chem. Int. Ed.* **2011**, *50*, 7438. b) Katayev, D.; Nakanishi, M.; Bürgi, T.; Kündig, E. P. *Chem. Sci.* **2012**, *3*, 1422.
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Organic Chemistry **495**

Synthesis of Oxindoles and Aza-oxindoles

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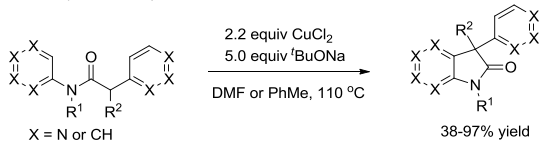
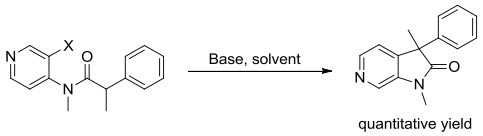
30 quai Ernest Ansermet, CH-1211 Geneva 4, Switzerland

Oxindoles and aza-oxindoles are common and important substructures in natural products and biologically active molecules. We here show that a robust, cheap and efficient copper mediated Csp^2-H, Csp^3-H coupling protocol gives access to oxindoles and aza-oxindoles in good to excellent yields [1,2]. The key step of this transformation is an intramolecular radical addition reaction (Scheme 1).



Scheme 1

In the course of these studies we have discovered a new route to access aza-oxindoles as shown below (Scheme 2). Optimization and mechanistic studies of this interesting rearrangement/cyclization protocol will be presented in this communication.



Scheme 2

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Organic Chemistry **496**

Getting control over Macrocyclization using Conformation Directing Groups

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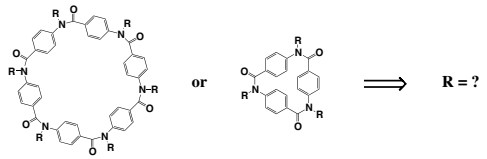
Shape persistent macrocycles are of special interest due to their rigid backbone, which results in many applications such as self-aggregation into columnar stacks for transport processes and separation, or usage as rigid scaffolds with well-defined cavities for catalytic or biomimetic applications, etc.[1] Since they occurred, their preparation represents a major challenge and has been intensively studied. Yet, most of the one-step cyclizations described so far leads to low yields and need many purification steps.



Here, we present the controlled one-step formation of tri- and hexa-oligo(*p*-benzamide) macrocycles from *N*-alkylated phenyl *p*-aminobenzoates. These monomeric building blocks contain conformation directing groups, whose nature determines whether they form cyclic trimers or hexamers in exceptionally high yields. The cyclization is presumably induced by the curved structure of the linear oligomer intermediate because of the favored cis conformation of the N-alkylated aromatic amide bond.[2]

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Organic Chemistry **497**

Amphiphilic oligopyrenes as units for supramolecular polymerization

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Department of Chemistry and Biochemistry, University of Bern
Freiestrasse 3, CH-3012 Bern

Oligoalkynylpyrenes ($\mathbf{S_n}$) in aqueous medium form well defined supramolecular assemblies under thermodynamic conditions. Temperature- and concentration-dependent UV/vis and fluorescence measurements can be used to probe the transition from the dissolved to the aggregated state. The obtained data suggest that polymerization occurs through a cooperative mechanism via nucleation step. The stability of aggregates is highly sensitive to variables such as temperature, concentration, ionic strength and presence of co-solvents. Morphology of these materials will be discussed.[1],[2],[3].

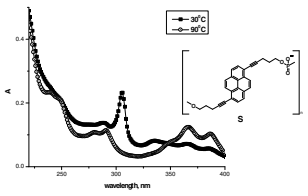

Fig.1. Temperature dependence of UV/vis for 10^{-6} M S_3 in aqueous medium (pH=7.05 10mMNaCl)

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Organic Chemistry **498**

The DNA three-way junction as a mould for tripartite chromophore assembly.

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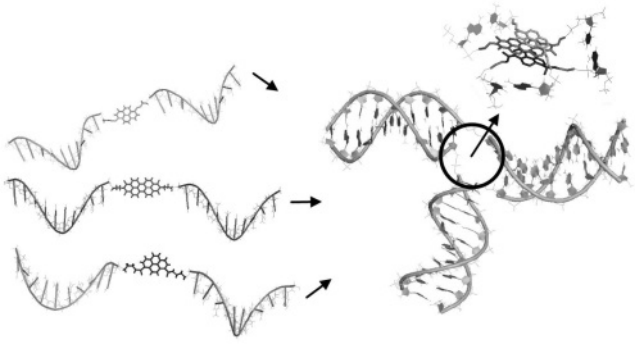
Department of Chemistry and Biochemistry, University of Bern
Freiestrasse 3, CH-3012 Bern

The DNA three-way junction (3WJ) is formed by three modified strands that are partially complementary in a pairwise fashion. The DNA 3WJ serves as a scaffold for the molecular organization of non-nucleosidic pyrene and perylene building blocks, located at the branch point of this higher order DNA structure. Depending on the composition of the tripartite assembly, the constructs possess distinct spectroscopic properties, ranging from pyrene monomer or excimer fluorescence to completely quenched tripartite aggregates. The spectroscopic properties of these aggregates are largely controlled by the nature of the inter-strand stacking interactions of the chromophores. [1] [2] [3]



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Organic Chemistry **499**

Bilaterally symmetric corannule derivatives

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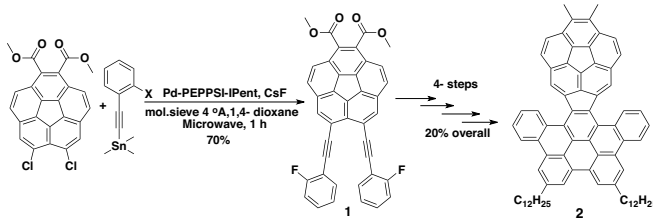
Institute of Organic Chemistry, University of Zurich, Winterthurstrasse 190, CH- 8057, Zurich, Switzerland

Corannulene is a bowl shaped molecule, with a large π-conjugated surface area and therefore great potential to form ordered materials.[1] Bilaterally symmetric diester diethynyl corannulene can function as a synthetically important intermediate[2] to achieve different classes of compounds with diverse scientific application. A corannulene-hemi- coronene hybrid from this intermediate is expected to be a bent-flat system. Photophysical and redox behavior of such a system should help better understand the π-conjugation behavior of a fullerene-graphene system. Appropriately tuned substituents in a corannulene-hemi-coronene architecture could be instrumental in the formation of supramolecular aggregates with material applications.

Herein, we report a synthesis of a corannulene-hemi-coronene compound (**2**), starting from dichloroacenaphthene. The diester-bis(phenylethynyl)-corannulene (**1**) is a crucial intermediate in this synthesis. Photophysical, redox and stacking behavior of this class of compounds as well as other possibilities from diester diethynyl corannulene strategic intermediates will be presented.



[1] Wu, Y. T.; Bandera, D.; Maag, R.; Linden, A.; Baldridge, K. K.; Siegel, J. S. *J. Am. Chem. Soc*. **2008**, *130*, 10729. [2] Wu, Y. T.; Hayama, T.; Linden, A.; Baldrige, K. K.; Siegel, J. S. *J. Am. Chem. Soc*. **2006**, *128*, 6870

Organic Chemistry **500**

Manganese Oxide Hybrid Nanocomposites Used as Mild Oxidant and Recyclable Catalyst

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Manganese oxide and silica manganese oxide nanoparticles were produced by flame spray pyrolysis and oxidized with sulphuric acid to generate particles which demonstrated enhanced oxidant properties when used under microwave irradiation (T=100-150°C, 300W, P=10-11bar for 1h). A variety of functionalized benzylic and allylic alcohols were transformed to the corresponding aldehydes in good yields within a short time and in high purity. Results were compared to the yields and purities of compounds obtained using commercially available manganese oxide (*Sigma-Aldrich*): under microwave conditions considerable loss of products were observed in most of the cases with the commercial reagent, comparable yields and quality of products were obtained at room temperature after 1-2 days. The activity of MnO_2 nanoparticles (pure and silica supported) was proven to be stable after half a year and more than one year. The new oxidant offered the advantage of a facile separation after reaction in addition to the shorter reaction time.

The FSP process was extended to the preparation of MnO_2/ Pd/ silica nanoparticles a new class of multifunctional catalytic composite materials. Several Sonogashira reactions, Suzuki couplings with bromo- and iodo aromatic derivatives demonstrated a comparable reactivity of the new catalyst to standard palladium catalysts. Hybrid nanocomposites could be used up to three times in a specific case of Suzuki reaction with phenylboronic acid without loss of activity. Tandem reactions involving first a C-C coupling followed by a controlled oxidation of alcohol to aldehyde are under current investigation as well as further characterization of the hybrid material.