CHIMIA

CHIMIA 2015, Volume 69
ISSN 0009-4293
www. chimia.ch

SCS
Swiss Chemical Society

Supplementa to Issue 7-8/2015

SCS Fall Meeting 2015

Poster Abstracts

Session of Organic Chemistry

September 4, 2015
Ecole Polytechnique Fédérale de Lausanne (EPFL)
http://scg.ch/fallmeeting/2015

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1-Alkynyltriazenes as Functional Analogues of Ynamides

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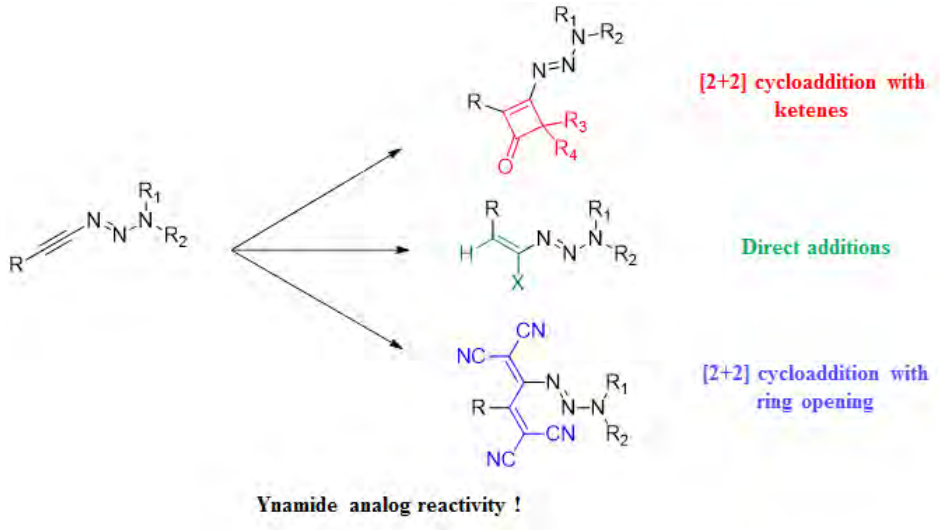
[1]EPF Lausanne

Recently, our group reported a procedure which allows preparing 1-alkynyltriazenes by a simple one-pot-reaction using nitrous oxide.[1] Here, we show that the chemical reactivity of 1-alkinyltriazenes parallels what has been observed for ynamides. The similarity in reactivity of these two classes of compounds is demonstrated by addition reactions with acids, by cycloaddition reactions with ketenes and tetracyanoethene. The presence of reactive triazene groups in the products allows subsequent transformations. Overall, our results suggest that 1-alkinyltriazenes should become valuable reagents in synthetic organic chemistry.



[1] G. Kiefer, T. Riedel, P. J. Dyson, R. Scopelliti and K. Severin, *Angewandte Chemie Int. Ed.*,**2015**, 54, 302.

Convergent Synthesis of Glycopeptide Dendrimer Biofilm Inhibitors based on the Chloroacetyl-Thioether-Cysteine (ClAc) Ligation

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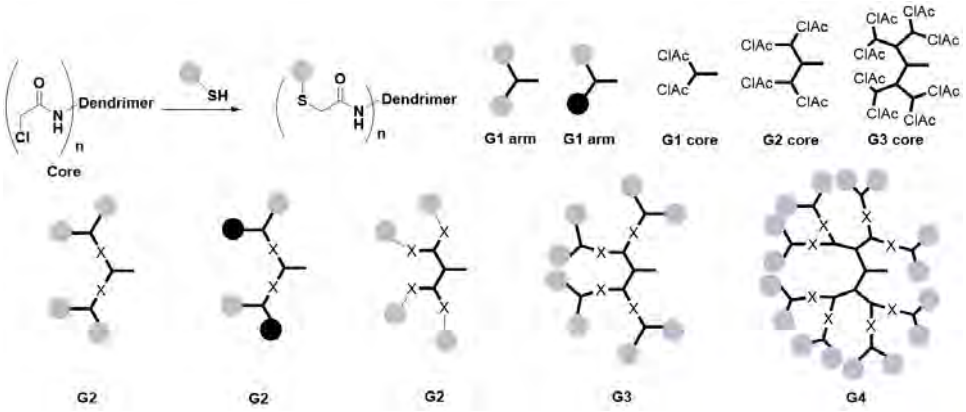
[1]University of Bern

Pseudomonas aeruginosa is one of the main causes of antibiotic-resistant nosocomial infections today.[1] These bacteria form biofilms, reinforcing their virulence. A biofilm consists of communities of bacteria attached to a solid surface and encased in an expolysaccharide matrix, a physical barrier to antibiotic penetration.[2] Several studies have shown the implication of the bacterial lectins LecA and LecB in biofilm formation, maturation and dispersal.[3] We recently reported several multivalent lectin inhibitors that also act as potent inhibitors of *Pseudomonas aeruginosa* biofilms. These inhibitors consist of a cationic 2nd generation peptide dendrimer core appended with four copies of a lectin-specific carbohydrate coupled to the four N-termini of the dendritic peptide sequence by amide bond formation on solid support.[4]



This synthetic approach required large quantities of carbohydrate building blocks and only gave limited isolated yields, calling for a revised synthetic strategy. Herein we report the convergent synthesis of glycopeptide dendrimers based on the chloroacetyl-thioether-cystein (ClAc) ligation between N-terminally chloroacetylated peptide dendrimers and thiol containing carbohydrate building blocks. The method proved suitable to prepare a variety of G2, G3 and G4 glycopeptide dendrimers including heteroglycoclusters displaying both the LecA specific beta-galactose and LecB specific alpha-fucose epitope. A broad survey of this expanded class of glycopeptide dendrimers led to the identification of a highly potent glycopeptide dendrimer with strong activity on biofilm formation and dispersal.

[1] Veesenmeyer, J. L., Hauser, A. R., Lisboa, T. Rello, J. *Crit. Care Med.* **2009**, 37, 1777–1786
[2] (a) Harmsen, M., Yang, L., Pamp, S. J. Tolker-Nielsen, T. *FEMS Immunol. Med. Microbiol.* **2010**, 59, 253–268; (b) Donlan, R. M. *Emerg. Infect. Dis.* **2002**, 8, 881–890.
[3] (a) Tielker, D. *et al. Microbiology* **2005**, 151, 1313–1323 (2005); (b) Diggle, S. P. *et al. Environ. Microbiol.* **2006**, 8, 1095–1104
[4] (a)Johansson, E. M. V *et al. Chem. Biol.* **2008**, 15**,** 1249–1257; (b) Kadam, R. U. *et al. Angew. Chem. Int. Ed. Engl.* **2011**, 50, 10631–10635; (c) Kadam, R. U. *et al. Chem. Eur. J.* **2013**, 19, 17054–17063; (d) Reymond, J.-L., Bergmann, M. Darbre, T. *Chem. Soc. Rev.* **2013**, 42, 4814–4822

Mechanism, Optimization and Scope studies of Rh(II) Catalyzed One-Step Multi-Component Macrocyclization Reactions

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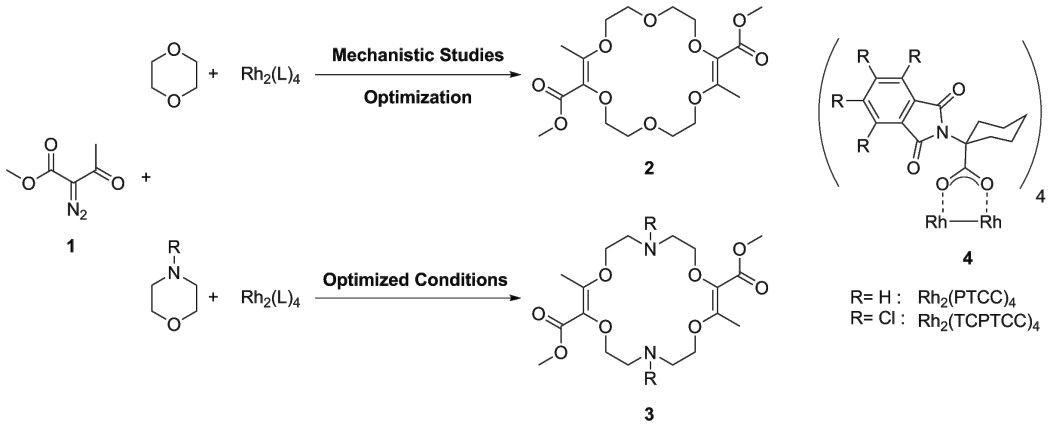
[1]University of Geneva

Recently, it has been shown that functionalized polyether macrocycles can be obtained in a single step by a [3+6+3+6] condensation of four components, and this under high concentration specifically (0.6 M).[1] Herein we present a mechanistic study of such a $Rh_2(Oct)_4$ catalyzed reaction of β-ketoesters diazo **1** and 1,4-dioxane that affords 18-membered macrocycle **2**. Kinetic information was gathered through NMR and FT-IR spectroscopy. Further information was obtained via labelled substrates and side products analysis by GC-MS, trapping experiments, intermediate characterization studies and finally in silico modelling.



Further kinetics studies showed the superior decomposition of β-ketoesters diazo **1** by Rh(II) complexes carrying carboxylic-phthalimide based ligands. Novel (achiral) complexes of type **4** were synthetized. Now, new conditions using only 0.001 mol% of these catalysts and affording 20 g of product are possible. Thanks again to mechanistic studies, conditions were also found for the use of protected morpholines affording important nitrogen-containing macrocycles **3**.

[1] (a) W. Zeghida, C. Besnard, J. Lacour, *Angew. Chem. Int. Ed*. **2010**, *49*, 7253. (b) D. Rix, R. Ballesteros Garrido, W. Zeghida, C. Besnard, J. Lacour, *Angew. Chem. Int. Ed*. **2011** , *50*, 7308. (c) R. Ballesteros Garrido, D. Rix, C. Besnard, J. Lacour, *Chem. Eur. J.* **2012**, *18*, 6626-6631. (d) M. Vishe, R. Hrdina, L. Guénée, C. Besnard, J. Lacour, *Adv. Synth. Catal.* **2013**, *355*, 3161-3169.

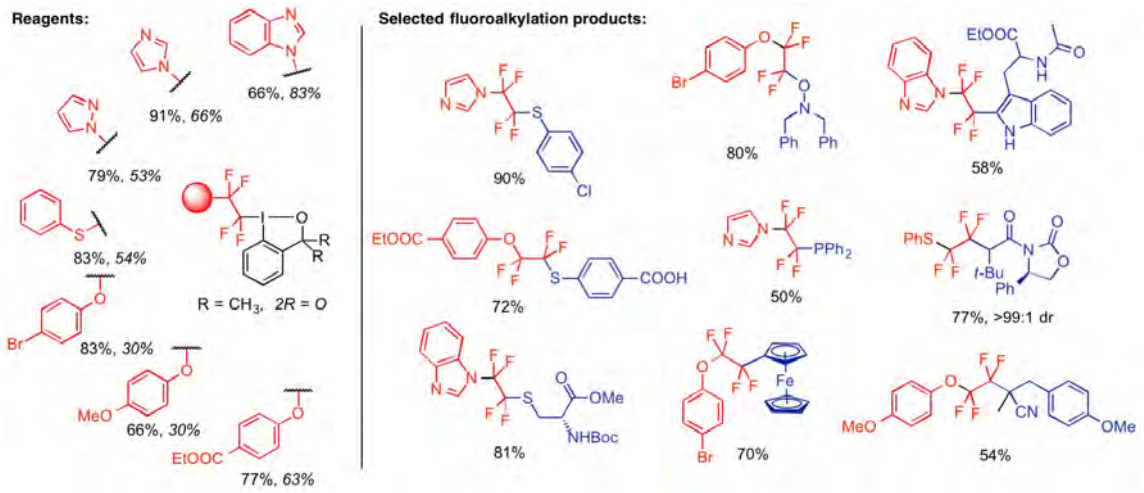
Synthesis and application of tetrafluoroethylation reagents based on hypervalent iodine

J. Vaclavik[1,2], V. Matoušek[1], P. Hájek[1], E. Pietrasiak[1], J. Charpentier[1], A. Budinská[2], Z. E. Blastik[2], A. Togni[1]*, P. Beier[2]*

[1]ETH Zurich, [2]Academy of Sciences of the Czech Republic

Organofluorine chemistry is currently at the forefront of interest for the development of pharmaceuticals, agrochemicals, materials, *etc*. Versatile methods for late stage selective introduction of fluoroalkyl moieties into complex molecules are therefore highly demanded.

This work is a further development of the increasingly popular trifluoromethylation reagents based on hypervalent iodine previously reported by Togni and co-workers.[1] These reagents are formally electrophilic *i.e.*, they react with various nucleophiles. We present here a set of analogous reagents by extending the CF_3 group to CF_2CF_2X (X = S-Ar, O-Ar, Ar_{het}). The applicability of these reagents was demonstrated on S, O, P and C-nucleophiles, providing unique structures, often not accessible by other approaches, such as nucleophilic fluoroalkylation or fluorination.



The shift from the terminal CF_3 group to CF_2CF_2X clearly adds a new dimension by the presence of a functional group at position 2 of the tetrafluoroethylene motif. Bearing this concept in mind, together with the fact that this type of reagents has an exceptionally high affinity for sulphur nucleophiles, we have also developed a reagent featuring a pyrene moiety for fluorescent labelling of sulphur-containing biomarkers, such as glutathione. The product of reaction with cysteine was stable even after the addition of 50 equivalents of octanethiol, demonstrating the irreversibile fluoroalkylation.

[1] J. Charpentier, N. Früh, A. Togni, *Chem. Rev.* **2015**, *115*, 650–682.

Synthesis of a Hydrogen-Bonded Quaterthiophene and its Use in Organic Field-Effect Transistors

B. Özen[1], J. Gebers[1], L. Hartmann[1], M. Schaer[1], H. Frauenrath[1]*

[1]EPF Lausanne

Supramolecular self-assembly represents a convenient pathway to create optoelectronic materials from monodisperse π-conjugated oligomers. Our work focuses on the preparation of novel oligothiophenes bearing substituents capable of hydrogen-bonding to enhance crystalline order, optimize the π-π stacking interaction, affect thin film morphology, and, thus, improve their electronic properties. Here, we present an improved synthetic pathway towards amine-substituted oligothiophenes and the synthesis of a quaterthiophene diacetamide. This hydrogen-bonded quaterthiophene was found to exhibit high charge carrier mobilities in organic field-effect transistors when deposited on octadecyltrichlorosilane (OTS) treated SiO_2 at elevated substrate temperatures and slow evaporation speeds.

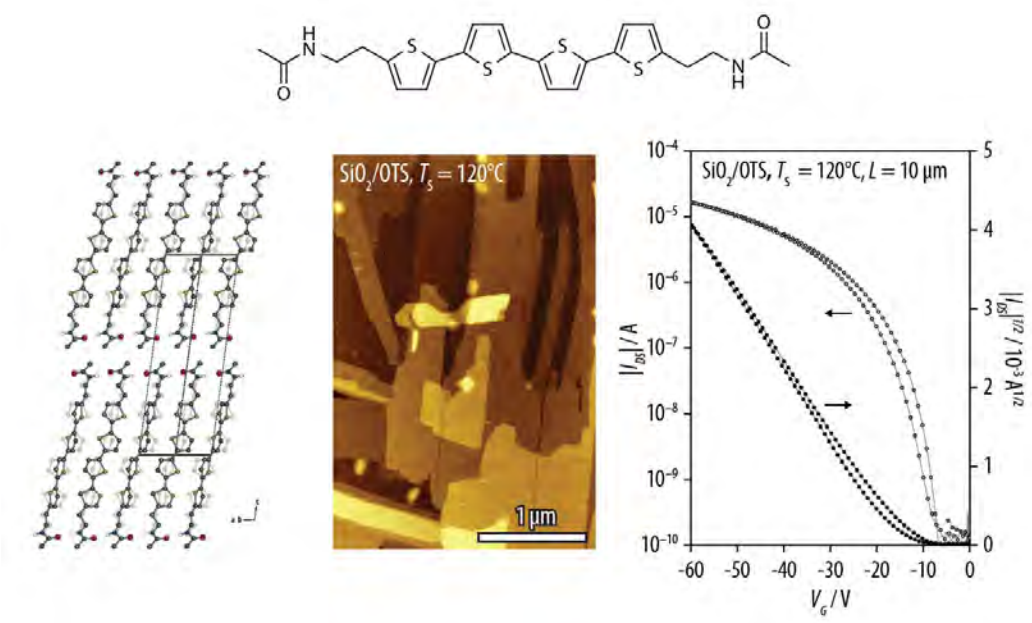


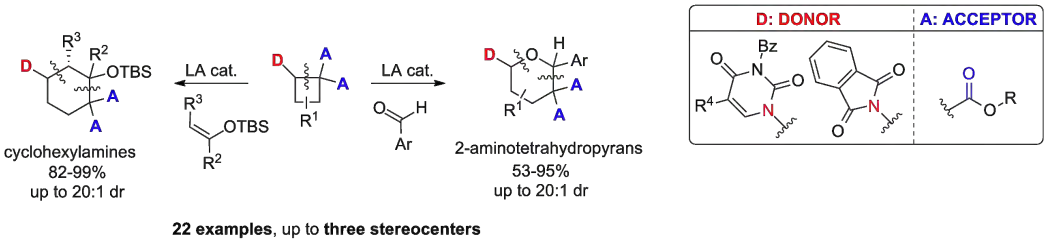
Figure1. Top: Structure of the quaterthiophene diacetamide; bottom: Single-crystal X-ray structure of quaterthiophene diacetamide (left), atomic force microscopy (AFM) height image of a film vapor-deposited onto a OTS-treated SiO_2 substrate (middle),transfer measurements for bottom-gate top-contact transistors (right).

[4+2]-Annulations of Aminocyclobutanes

D. Perrotta[1], S. Racine[1], F. de Nanteuil[1], J. Waser[1]*

[1]EPF Lausanne

In the domain of small ring chemistry, donor-acceptor cyclopropanes have been widely used in annulations to generate complex cyclic structures. However, the use of their analogues 4-membered rings have been less investigated up to now. Herein we report for the first time the use of donor-acceptor aminocyclobutanes in [4+2]-annulations with aldehydes and silyl-enol ethers.[1] The 2-aminotetrahydropyrans and cyclohexylamines are recurring motifs in biologically active molecules. [4+2]-annulation of substituted aminocyclobutanes with aldehydes delivered products bearing three stereocenters, using scandium triflate or iron trichloride as catalyst. The use of thymine- or fluorouracil-substituted cyclobutanes gave direct access to six-membered ring nucleoside analogues. Finally, the [4 + 2]-annulation between aminocyclobutanes and silyl enol ethers led to the corresponding cyclohexylamines.



[1]Perrotta, D.; Racine, S.; Vuilleumier, J.; de Nanteuil, F.; Waser J.*OL*,**2015**, 17, 1030.

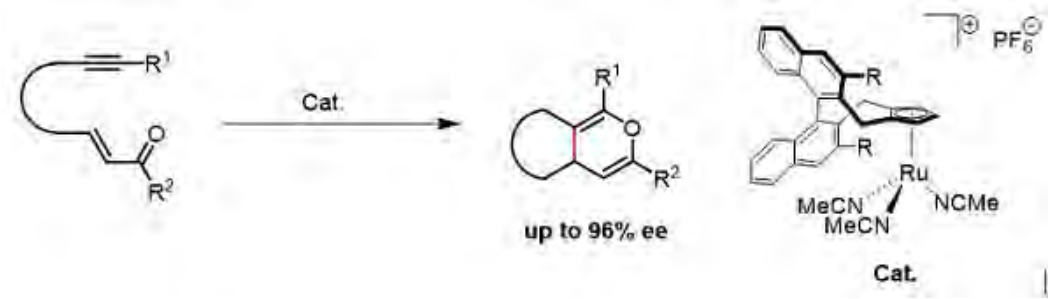
Synthesis of chiral Ruthenium-cyclopentadienyl complexes and application to formal [4+2] cyclizations of yne-enones

D. Kossler[1], N. Cramer[1]*

[1]EPF Lausanne

Ruthenium catalyzed cycloisomerizations offer a rapid access to complex molecular frameworks in an atom economical fashion.[1] Therefore the cationic $[CpRu(MeCN)_3]PF_6$ complex found widespread application in organic synthesis. The endeavor to conduct these transformations in an enantioselective manner led to several ligand design approaches, albeit resulting in mediocre selectivities. Recently our group pioneered in the development of highly efficient chiral Cp ligands for late transition metal catalysis[2] and we intend to explore their potential in combination with various metals.

Ruthenium (II) complexes derived from a 3,3 disubstituted *R*-Binol backbone proved to catalyze the formal [4+2] cyclization of yne-enones to the corresponding pyrans in high enantioselectivity.[1] This particular transformation delivers a sensitive framework in a mild way from easily accessible starting materials. Moreover, these products provide valuable building blocks for follow up functionalizations.



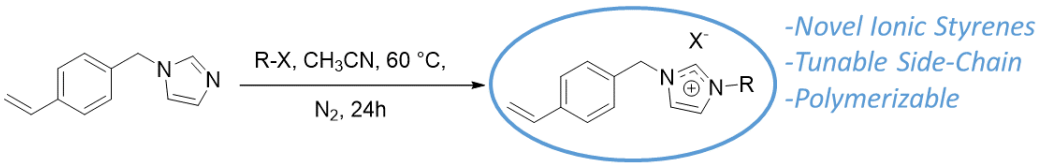
[1] B. M. Trost, M. U. Frederiksen, M. T. Rudd, *Angew. Chem. Int. Ed.* **2005**, *44*, 6630–6666.
[2] a) B. Ye, N. Cramer, *Science* **2012**, *338*, 504-506 b) B. Ye, N. Cramer, *J. Am. Chem. Soc.* **2013**, *135*, 636-639.
[3] B. M. Trost, R. E. Brown, F. D. Toste, *J. Am. Chem. Soc.* **2000**, *122*, 5877-5878.

Synthesis, Characterization and Application of Styrene-Functionalized Imidazolium Salts

F. D. Bobbink[1], P. Dyson[1]*

[1]EPF Lausanne

Imidazolium-based salts are an important class of ionic liquids, as they are used for many applications such as solvents, catalysts, nanoparticle stabilizers and others. We synthesized and characterized imidazolium salts containing a polymerizable styrene group, and a functionalized, tunable side-chain (scheme 1). Starting from a procedure described in literature [1], 4-vinylbenzylimidazole (VIm) is easily prepared. Quaternization of VIm with a suitable partner allows the synthesis of a library of new, functionalized imidazolium-based ionic liquids, systematically containing one styrene unit. A straightforward purification method consists in sonication of the salt in ethyl acetate or diethyl ether to afford a pure ionic liquid in high yields. The obtained ionic liquids were evaluated as catalysts for the cycloaddition of carbon dioxide to epoxides. In addition, these ionic liquids can easily be polymerized in ethanol under using AIBN as radical initiator.



Impurities removed by precipitation/sonication in apolar solvent:
-Efficient
-Simple
-Based on solvent affinities

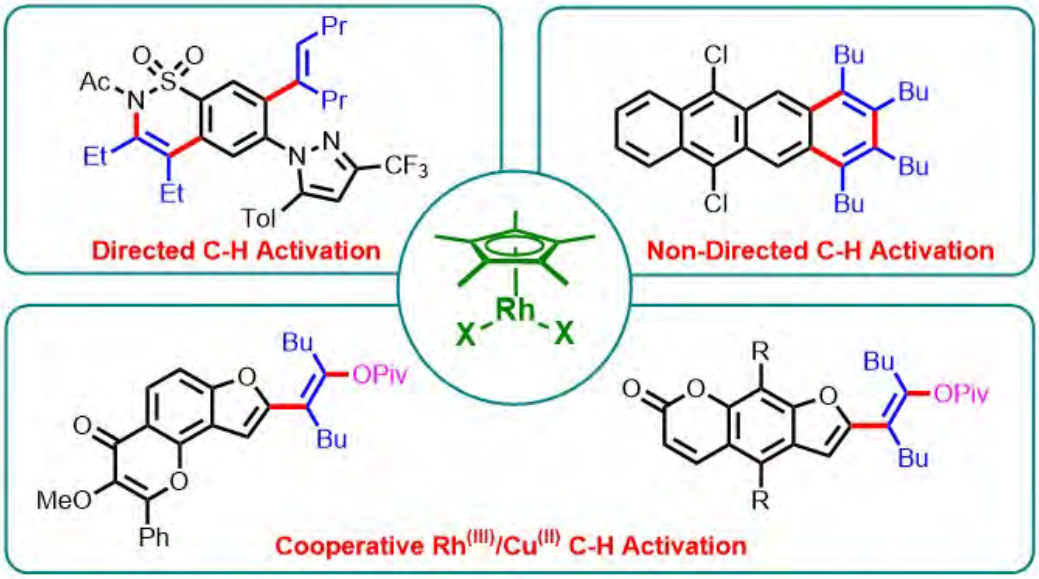
[1] Matthew D. Green, Jae-Hong Choi, Karen I. Winey, Timothy E. Long, *Macromolecules,* **2012**, 45, 4749–4757.

Rhodium(III)-Catalyzed C-H Activation Rapid Access to Versatile Organic Molecules

M. V. Pham[1], N. Cramer[1]*

[1]EPF Lausanne

During the past decade, transition-metal-catalyzed C–H activation has emerged as an attractive strategy to prepare organic building blocks in a step and atom-economical fashion. An impressive number of transformations aimed at directly installing new C-C or C-X bonds have been developed based on this strategy.[1] Herein, we demonstrated the wide application of Cp*Rh$^{(III)}$ catalyst in the synthesis of highly valuable organic compounds as exemplified by arylsultams, polycyclic aromatic hydrocarbons and *trans*-enol esters *via* directed C-H activation and non-directed C-H activation.[2, 3, 4]



[1] G. Song, F. Wang, X. Li, *Chem. Soc. Rev.* **2012**, *41*, 3651.
[2] M. V. Pham, B. Ye, N. Cramer, *Angew. Chem. Int. Ed.* **2012**, *51*, 10610 (Highlighted in *Synfacts*, **2012**, *8*, 1299).
[3] M. V. Pham, N. Cramer, *Angew. Chem. Int. Ed.* **2014**, *53*, 3484. (Highlighted Synfact of the month May, **2014**).
[4] M. V. Pham, N. Cramer, *Angew. Chem. Int. Ed.* **2014**, *53*, 14575.

Chiral Cyclopentadienyl-Iridium Complexes as Catalysts for Cycloisomerizations of N-tethered 1,6-Enynes

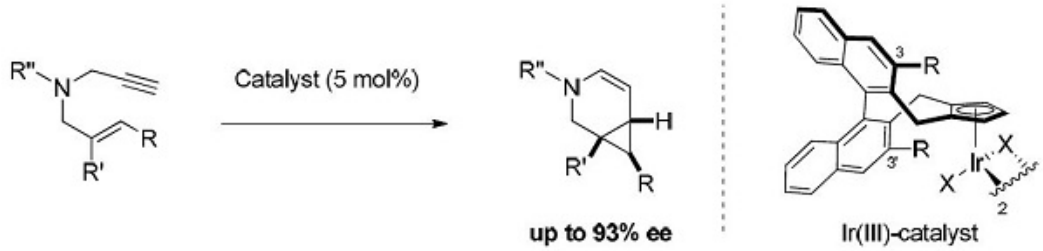
M. C. Dieckmann[1], Y. Jang[1], N. Cramer[1]*

[1]EPF Lausanne

Cyclopentadienyl (Cp) ligands represent an ubiquitous motif in organometallic chemistry. However, for several decades the lack of efficient chiral Cp-versions has limited the design of novel catalysts for asymmetric transformations. Recently, our group developed chiral disubstituted Cp-ligands drawing their chirality from a 3,3'-substituted Binol-backbone.[1]

We present new members of this ligand family and report the synthesis of the corresponding iridium-(III)-complexes. To demonstrate the value of these new complexes as efficient catalysts, enantio-selective cycloisomerizations were investigated.[2]

In detail, *N*-tethered 1,6-enynes were cycloisomerized under mild conditions via a *6-endo-dig*-pathway to 3-azabicyclo[4.1.0]heptenes as single cyclopropane diastereomers and in high enantioselectivities up to 93% *ee*.



[1] a) B. Ye, N. Cramer, *Science* **2012**, *338*, 504-506; b) B. Ye, N. Cramer, *J. Am. Chem. Soc.* **2013**, *135*, 636-639.
[2] a) E. Benedetti, A. Simonneau, A. Hours, H. Amouri, A. Penoni, G. Palmisano, M. Malacria, J.-P. Goddard, L. Fensterbank, *Adv. Synth. Catal.* **2011**, *353*, 1908-1912; b) I. D. G. Watson, F. D. Toste, *Chem. Sci.*, **2012**, *3*, 2899-2919.

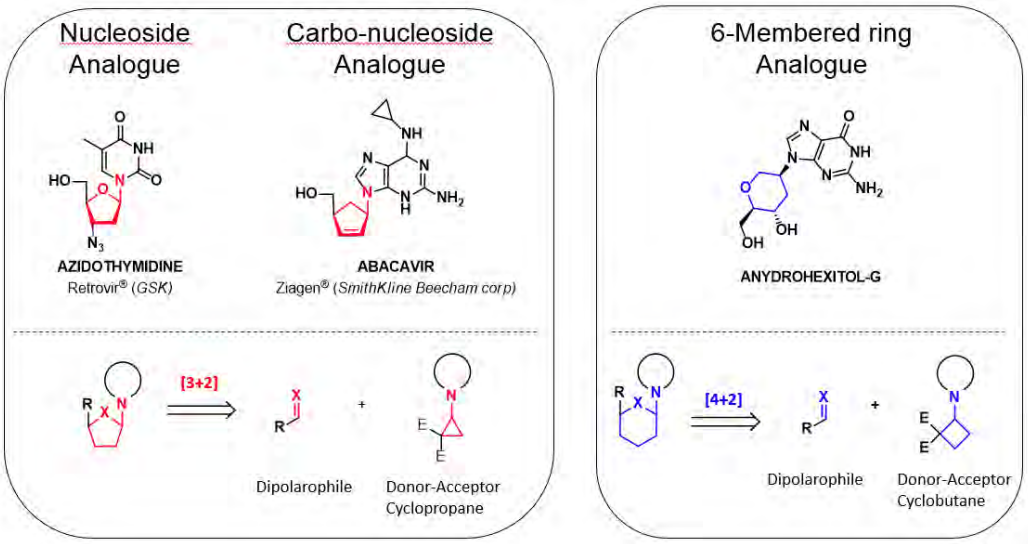
Annulation of strained Rings, a Usefull Tool for the Synthesis of Nucleoside Analogues

S. Racine[1], J. Waser[1]*

[1]EPF Lausanne

Nucleosides and carbonucleosides analogues are widely used as drugs against a large range of disorders such as HIV, malaria or tuberculosis. Due to the emergence of resistance against marketed drugs as reported by the World Health Organisation, there is a high interest in the discovery of new bioactive compounds against these diseases.

Our group is investigated chemical transformation such as annulation reaction of polarized small ring molecules (donor-acceptor cyclopropanes and donor-acceptor cyclobutanes)[1-4], proceeding through controlled ring opening and strain release. Herein, we describe a highly convergent and efficient formal [3+2] annulation reaction between nucleobase-substituted cyclopropanes and dipolarophiles (ketones, aldehydes and enolethers), giving a direct access to nucleoside and carbonucleoside analogues.[5] We further report the extension of our strategy to the preparation of six-membered ring nucleoside analogues via a [4+2] annulation reaction.[6]



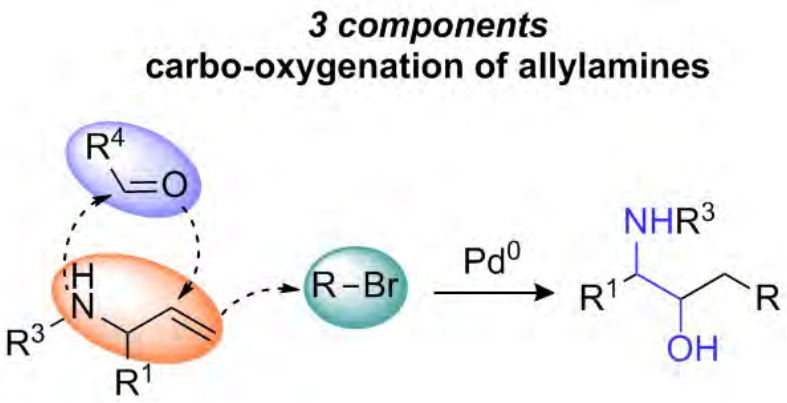
[1] De Nanteuil, F.; Waser, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 12075.
[2] Benfatti, F.; De Nanteuil, F.; Waser, J. *Org. Lett.* **2012**, *14*, 386.
[3] Benfatti, F.; De Nanteuil, F.; Waser, J. *Chem. Eur. J.* **2012**, *18*, 4844.
[4] De Nanteuil, F.; Waser, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 9009.
[5] Racine, S.; De Nanteuil, F., Serrano, S.; Waser, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 8484.
[6] Perrotta, D.; Racine, S.; Vuilleumier, J.; De Nanteuil, F.; Waser, J. *Org. Lett.* **2015**, *17*, 1030–1033.

Vicinal Amino Alcohols Synthesis from Allyl Amines via in Situ Tether Formation and Pd-Catalyzed Carboetherification

U. Orcel[1], J. Waser[1]*

[1]EPF Lausanne

Vicinal amino alcohols are common stuctural units both in drugs and natural products. Herein, we report an unprecedented 3-component tethered carbo-etherefication of allylamines for their synthesis, using trifluoroacetaldehyde as in situ tether. Alkynyl, aryl and vinyl groups could be successfully introduced in good yield and diastereoselectivity and with high functional group tolerance. The products obtained could be readily and selectively deprotected to access either the free amine or alcohol, thus demonstrating their usefulness.



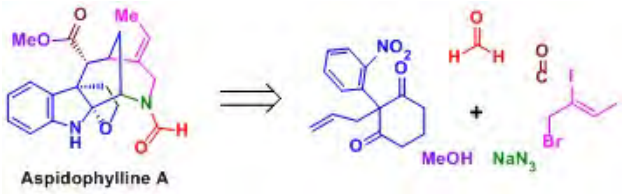
U. Orcel, J. Waser *Angew. Chem. Int. Ed.* **2015,** *127,* 5339

Total Synthesis of (±)-Aspidophylline A

W. Ren[1], Q. Wang[1], J. Zhu[1]*

[1]EPF Lausanne

Aspidophylline A was isolated from Malayan *Kopsia singapurensis* by Kam and co-workers in 2007 and was found to reverse drug resistance in drug-resistant KB cells.[1] Structurally, it is a cagelike pentacyclic compound that includes a highly substituted cyclohexane with five contiguous stereocenters, an embedded fused furoindoline ring, and a bridged [3.3.1] azabicycle. It belongs to the family of akuammiline monoterpene indole alkaloids, which includes strictamine, vincorine, and scholarisine A, among others. The fascinating molecular architecture in conjunction with its interesting biological activity made aspidophylline A a privileged synthetic target.



We elaborate here the total synthesis of aspidophylline A, which has been accomplished in 14 steps starting from known 2-allyl-2-(o-nitrophenyl)cyclohexane-1,3-dione.[3] Key features of our synthesis include: 1) rapid access to a fully functionalized dihydrocarbazole through the desymmetrization of readily available 2-allyl-2-(o-nitrophenyl)cyclohexane-1,3-dione; 2) an intramolecular azidoalkoxylation of an enecarbamate to install both the furoindoline ring and the azido functionality; and 3) an intramolecular Michael addition for the construction of the 2-azabicyclo[3.3.1]nonane ring system.

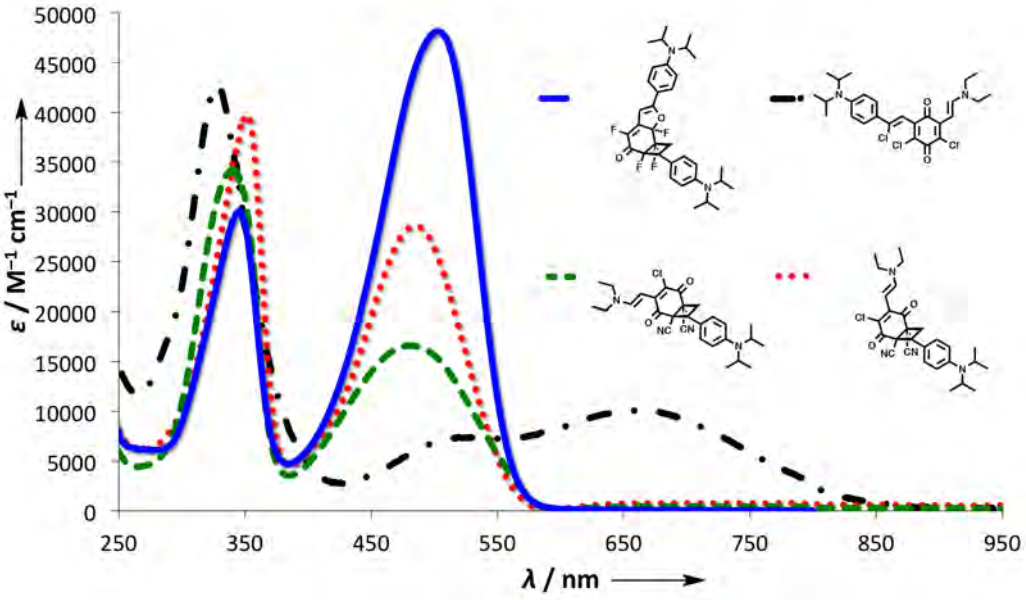
[1] G. Subramaniam, O. Hiraku, M. Hayashi, T. Koyano, K.Komiyama, T.-S. Kam, *J. Nat. Prod.* **2007**, *70*, 1783-1789.
[2] a) L. Zu, B.W. Boal, N. K. Garg, *J. Am. Chem. Soc.* **2011**, *133*, 8877-8879; b) M. Teng, W. Zi, D. Ma, *Angew. Chem. Int. Ed.* **2014**, *53*, 1814-1817.
[3] W. Ren, Q.Wang, J. Zhu, *Angew. Chem. Int. Ed.* **2014**, *53*, 1818-1821.

Synthesis and Properties of Quinone-Type Push–Pull Chromophores

C. Dengiz[1], C. Prange[1], N. Trapp[1], L. Ruhlmann[2], C. Boudon[2], F. Diederich[1]*

[1]ETH Zurich, [2]University of Strasbourg

The chemistry of quinones has been broadly explored since this class of compounds includes important natural products and drugs.[1] Modification of the core quinone structures by the introduction of donors creates sophisticated push–pull chromophores displaying intense intramolecular charge-transfer transitions.[2] This makes them crucial organic compounds in the materials science field. Herein, we report the synthesis of a series of quinone-based push–pull chromophores to define structure-property and structure-reactivity relationships. Moderate to intense charge transfer bands (ε values between 10000 and 54000 $M^{-1}\,cm^{-1}$) with λ_{max} values in the range of 479–657 nm (2.59–1.89 eV) were obtained for the synthesized chromophores. The push–pull chromophores are also potential candidates for use in materials with non-linear optical properties.[3]



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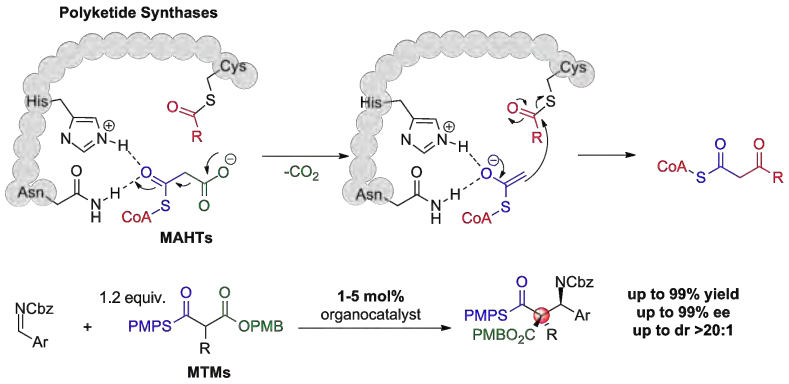
[3] Kato, S.-i.; Bells, M. T. R.; La Porta, P.; Schweizer, W. B.; Boudon, C.; Gisselbrecht, J.-P.; Biaggio, I.; Diederich, F. *Angew. Chem. Int. Ed.* **2010**, *49*, 6207–6211.

Stereoselective Organocatalytic Synthesis of Oxindoles with Adjacent Tetrasubstituted Stereocenters

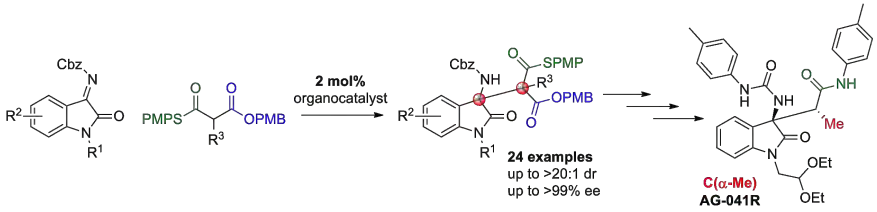
O. D. Engl[1], H. Wennemers[1]*

[1]ETH Zurich

Thioesters are versatile building blocks for subsequent transformations into other functional groups such as ketones, aldehydes or amides. An attractive method to introduce thioesters is by reacting thioester enolates with appropriate electrophiles. The formation of such thioester enolates under mild organocatalytic conditions is, however, not trivial due to the low acidity of the α-proton, and often requires unfavorable conditions. Nature utilizes malonic acid half thioesters (MAHTs) as thioester enolate equivalents in the biosynthesis of fatty acids and polyketides. MAHTs have also been used in organic synthesis but suffer from uncontrolled decarboxylation and require the use of large amounts of catalyst (›10 mol%) and carefully chosen reaction conditions.[1] Our group introduced mono thiomalonates (MTMs) as protected variants of MAHTs, which react in a more controlled fashion and require significantly lower catalyst loadings than MAHTs.[2-5] MTMs bear an easily removable protecting group on the ester moiety, which provides for controlled nucleophilic reactivity at the *α*-carbon and decarboxylation occurs only upon removal of the protecting group.



In the present study, MTMs are used as versatile thioester nucleophiles in a highly enantioselective, organocatalytic addition to isatin-derived N-Cbz ketimines.[6] This method affords 3-substituted 3-amino-2-oxindoles containing two adjacent tetrasubstituted stereocenters and only requires a low catalyst loading of 2 mol%. The appropriate choice of catalyst allows for the selective formation of both enantiomers in excellent yields and stereoselectivities. Furthermore, this method was successfully applied to the synthesis of a previously inaccessible C(*α*-Me)derivative of a gastrin/cholecystokinin-B receptor antagonist AG-041R.



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[5] Engl, O. D.; Fritz, S. P.; Käslin, A.; Wennemers, H. *Org. Lett.* **2014**, *16*, 5454-5457.
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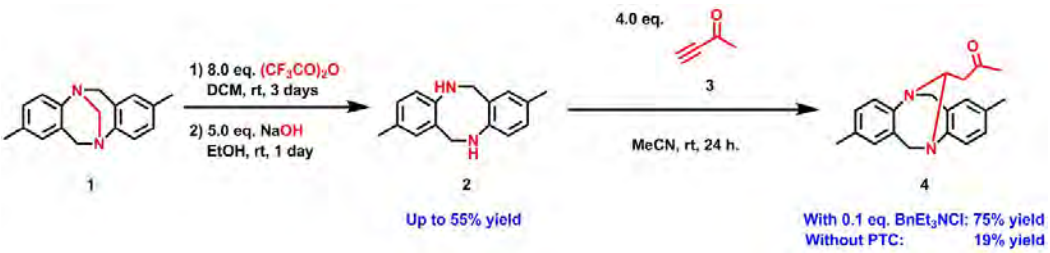
Synthesis of Tröger's Base Analogues via a Phase-Transfer-Catalyzed Double Aza-Michael Reaction Under Base-Free Conditions

T. Kamiyama[1], J. Cvengros[1]*

[1]ETH Zurich

Tröger's base (**1**) is a rare example of a compound containing configurationally stable stereogenic nitrogens due to a high inversion barrier. Its derivatives have been used for various applications including catalysis and molecular recognition [1].

Tetrahydrodiazocine (**2**), which can be prepared by removal of the methylene bridge in **1**, was shown to undergo double aza-Michael additions with electron-deficient alkynes, giving Tröger's base derivatives with various functional groups on the bridge [2]. We have evaluated analogous alkynes, such as 3-butyn-2-one (**3**) and witnessed a reduced reactivity in the double aza-Michael reaction. The screening revealed that a phase-transfer-catalyst (PTC) significantly enhances the rate of the transformation. Interestingly, no additional base is required [3]. The complete study, scope, limitations and preliminary results with chiral ammonium salts will be presented.



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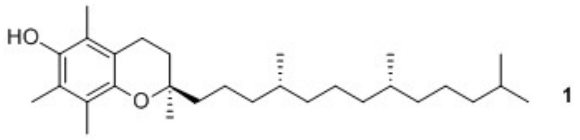
[2] A. Lauber, B. Zelenay, J. Cvengroš *Chem. Comm.* **2014**, *50*, 1195 – 1197.
[3] S. Shirakawa, K. Maruoka *Tetrahedron Letters* **2014**, *55*, 3833 – 3839.

Towards a Short Synthesis of (R,R,R)-α-Tocopherol

T. Netscher[1], U. Létinois[1], S. Ackermann[1], W. Bonrath[1], J. Medlock[1]

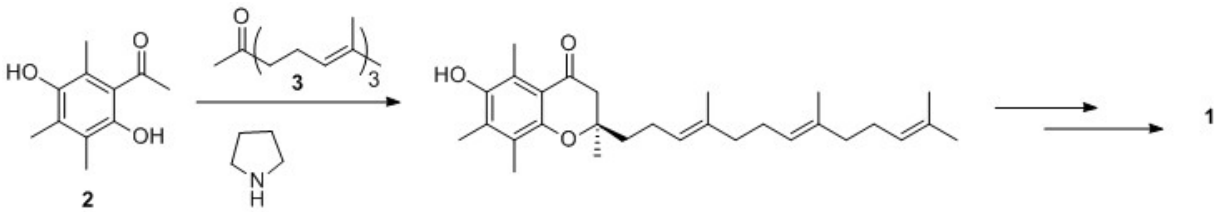
[1]DSM Nutritional Products, Basel

The most bioactive compound within the vitamin E class is (*R,R,R*)-α-tocopherol **1**. The industrially manufactured product is a mixture of all eight α-tocopherol stereoisomers, as known synthetic approaches to the optically pure (*R,R,R*)-α-tocopherol are lengthy and complicated.[1]



An achiral organocatalytic approach to chromans had been published in 1978 by Kabbe and Heitzer.[2] Tocotrienols were accessible in good yields using 2-acetyl-3,5,6-trimethylhydroquinone **2** and farnesyl acetone **3** as starting materials.

In the present contribution we disclose how we achieved a very short synthesis of optically enriched (*R,R,R*)-α-tocopherol **1** starting from industrially available 2,3,5-trimethylhydroquinone. By the use of chiral organocatalysts having a pyrrolidine backbone and application of Pfaltz's methodology for asymmetric hydrogenation of unfunctionalized olefins [3] we obtained a stereoisomerically enriched (*R,R,R*)-α-tocopherol in only four steps and very good yield. We discuss the influences of various reaction conditions, mechanistic studies as well as the limitations of this approach.



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Chiral verdazyl radicals for metal-organic functional assemblies

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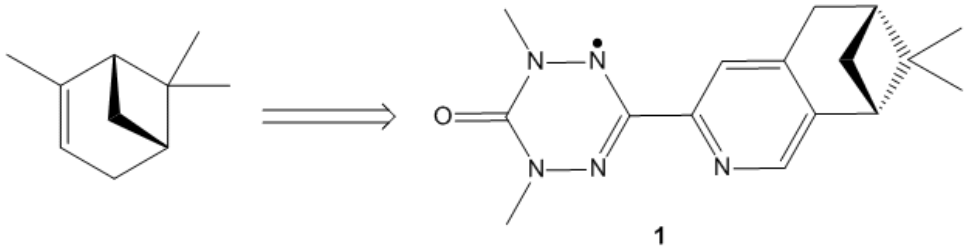
[1]Haute Ecole d'Ingénierie et d'Architecture Fribourg, [2]Université Joseph Fourier Grenoble

The molecule-based magnetic systems attracted much attention in the last two decades for their potential applications in the field of materials possessing properties like spin-crossover, single object or long range magnetic ordering. Many (supra)molecular coordination assemblies involving paramagnetic metal ions have been reported. However, only few examples containing enantiopure metal centers allowing the study of magneto-chiral effect have been reported. Recently it has been shown that the use of radicals instead of usual ligands can enhance the exchange interaction and lead to efficient single molecule magnets. Verdazyl type ligands are promising organic radicals example because their complexes revealed high values of the metal-radical magnetic interactions.[1]



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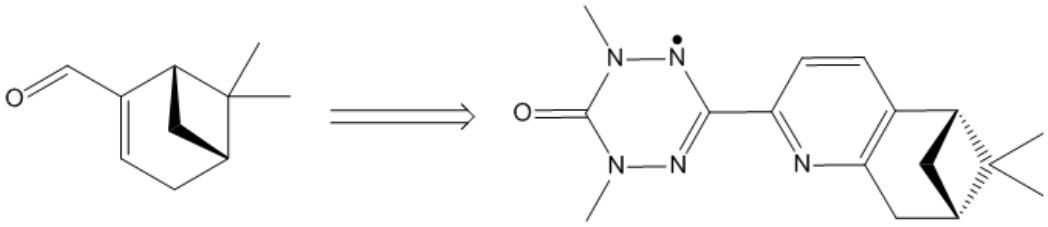

2

Using the well-known approach based on diastereoselective synthesis of metalla-supramolecular compounds based on chiral induction [2] we present here the synthesis and characterization of the first chiral pyridine verdazyl derivatives. Starting from the chiral pool (+)-α-pinene or (1R)-(-)-myrtenal we developed multistep syntheses leading to the compounds **1** and **2.** The complete characterization of these two compounds[3]as basis for a large library of ligands designed to fulfill various coordination numbers and geometries will be presented.

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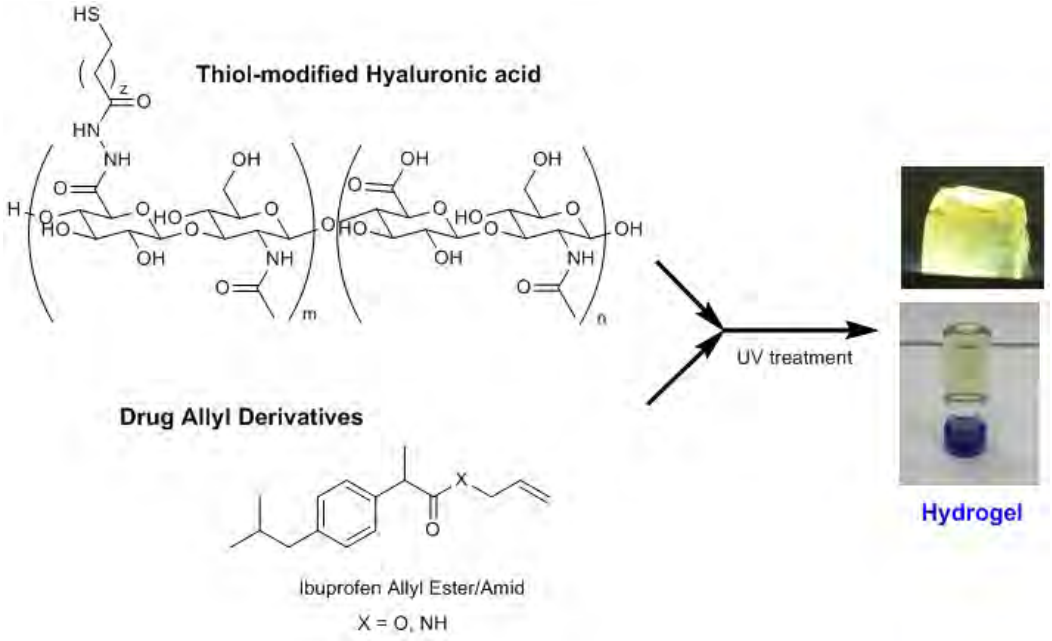
[3] Y. Mongbanziama, O. Mamula Steiner *et al*., manuscript in preparation; Y. Mongbanziama: Travail de Bachelor, Max Lüthi prize of the Swiss Chemical Society (**2014**).

Hyaluronic Acid-Based Hydrogels for Drug Delivery

R. Marti[1,2], D. Meyer[1], Y. Stampfli[1], P. Brodard[1]

[1]School of Engineering and Architecture of Fribourg, [2]Institute ChemTech

Today, hydrogels are widely used as smart materials in tissue engineering and biomedical applications [1]. In our work we use hyaluronic acid (HA), which is one of the main components of the extracellular matrix of the skin and cartilage. Typically HA-based hydrogels are prepared by cross-linking via thiol Michael reaction or radical thiol-ene reaction [2].



Here, we present our work on the synthesis of specially designed hyaluronic acid and PEG building blocks for the preparation of hydrogels by UV-mediated radical thiol-ene reaction [2]. These HA-based hydrogels were further modified to obtain drug delivery systems by using functionalized drugs like Ibuprofen allyl ester or allyl amide. The synthesis, physical characterization and as well as preliminary drug release tests of these novel Ibuprofen drug delivery systems are discussed.

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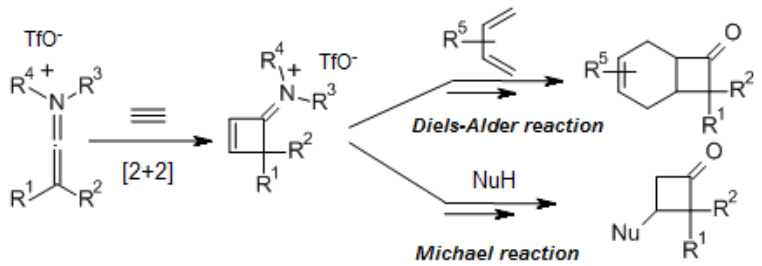
Efficient Access to Functionalized Cyclobutanone Derivatives Using Cyclobuteniminium Salts as Highly Reactive Michael Acceptors and Dienophiles

A. Lumbroso[1], A. Kolleth-Krieger[1], P.-Y. Dakas[1], S. Catak[2], A. De Mesmaeker[1]*, S. Sulzer[1]*

[1]Syngenta Crop Protection AG, Switzerland, [2]Bogazici University, Department of Chemistry, Istanbul, Turkey

An efficient access to cyclobutanone derivatives has been developed *via* a “one-pot” [2+2] / [4+2] or [2+2] / Michael addition sequence involving keteniminium and cyclobuteniminium salts as key intermediates. A broad range of novel cyclobuteniminium salts have been prepared *via* [2+2] cycloaddition between keteniminium salts and alkynes. The resulting [2+2] adducts were then further transformed by Diels-Alder reaction and Michael addition with various dienes and nucleophiles respectively to afford cyclobutanone derivatives in good yields. A density functional theory (DFT) based computational study has been performed to investigate the unique reactivity of cyclobuteneiminium salts.



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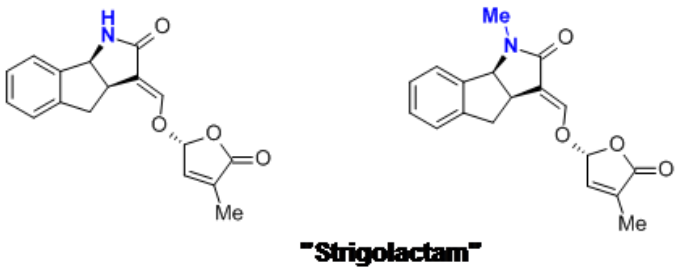
Strigolactam: New potent strigolactone analogues for the germination of Orobanche Cumana

A. Lumbroso[1], M. Lachia[1], P.-Y. Dakas[1], P. Jung[1], C. Screpanti[1], S. Rendine[1], R. Fonne-Pfister[1], A. De Mesmaeker[1]*

[1]Syngenta Crop Protection AG, Switzerland

Very recently, strigolactones have been conclusively identified as phytohormones.[1-4] The progresses achieved in this field are culminating in the identification of the molecular receptors involved in the signal transduction mechanism. The exact mechanism of the mode of action of strigolactones still remains to be fully elucidated and we were interested to gain some insight into the mechanism of action of strigolactones by selectively modifying the reactivity of the lactone C-ring.[5] Therefore, we report here the synthesis of new strigolactams and their surprisingly good activity on the germination of Orobanche cumana parasitic weed seeds.



"Strigolactam"

[1] E. Villedieu-Percheron, M. Lachia, P. M. J. Jung, C. Screpanti, R. Fonné-Pfister, S. Wendeborn, D. Zurwerra, A. De Mesmaeker, *Chimia*, **2014**, *68*, 654-663
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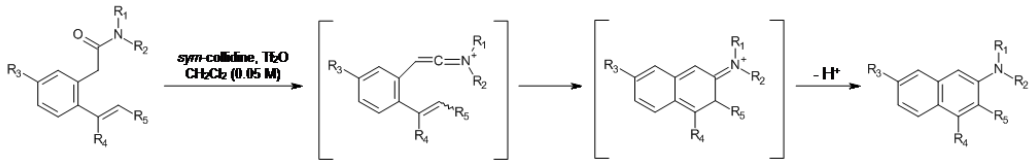
[4] M. Lachia, P.-Y. Dakas, A. De Mesmaeker, *Tetrahedron Lett.* **2014**, *55*, 6577-6581
[5] M. Lachia, H. C. Wolf, P. M. J. Jung, C. Screpanti, A. De Mesmaeker,*Bioorg. Med. Chem. Lett*. **2015**, *25*, 2184-2188

6π/10π-electrocyclization of ketene-iminium salts for the synthesis of substituted naphthylamines

A. Kolleth-Krieger[1], E. Villedieu-Percheron[1], S. Catak[2], D. Zurwerra[1], R. Staiger[1], M. Lachia[1], A. Lumbroso[1], S. Sulzer[1], A. De Mesmaeker[1]*

[1]Syngenta Crop Protection AG, Switzerland, [2]Bogazici University, Department of Chemistry, Turkey

An efficient method to access highly substituted naphthylamines has been developped involving a vinyl ketene-iminium salt which reacts via a 6π/10π-electrocyclization. This reaction proceeds starting from easily accessible amides which generate the corresponding ketene-iminium salts and finally an elecrocyclization lead to naphthylamines after rearomatization. Various substituents on the nitrogen, on the aromatic ring and also on the vinyl moiety are well tolerated. Moreover, the 6π/10π-electrocyclization involving the ketene-iminium salt has been rationalized by DFT calculations where it has been shown that this step is highly exergonic and has a low barrier of activation.

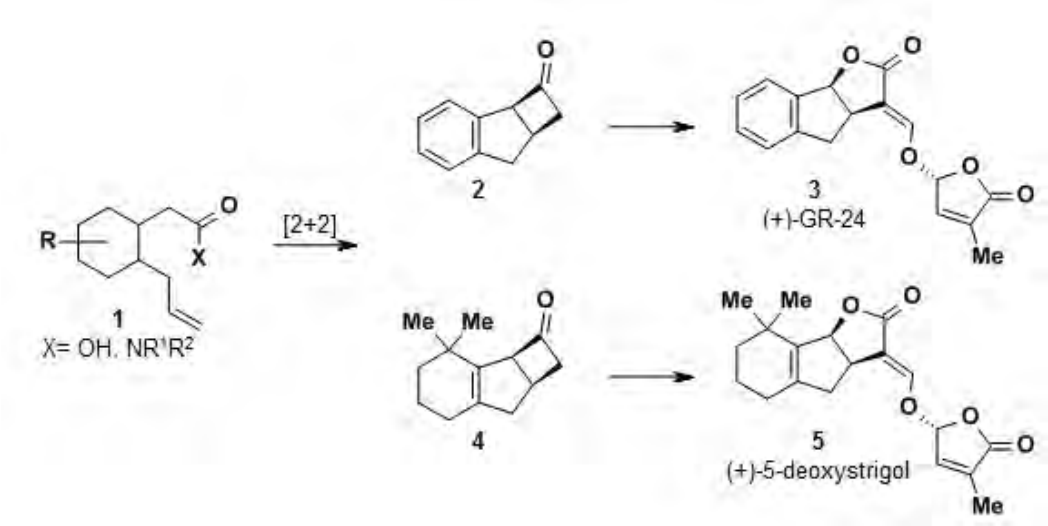


[1] Emmanuelle Villedieu-Percheron, Saron Catak, Didier Zurwerra, Roman Staiger, Mathilde Lachia, Alain De Mesmaeker, *Tetrahedron Letters*, **2014**, 2446-2449.

Asymmetric synthesis of (+)-GR-24 and the four stereoisomers of (+)-5-deoxystrigol using [2+2]-cycloadditions of ketene-iminiums to olefins

P.-Y. Dakas[1], M. Lachia[1], A. Lumbroso[1], P. Jung[1], S. Rendine[1], R. Fonne-Pfister[1], C. Screpanti[1], A. De Mesmaeker[1]*

[1]Syngenta Crop Protection AG, Switzerland



An intramolecular [2+2]-cycloaddition between ketene-iminium salts and olefins was developed as a key step for the asymmetric synthesis of (+)-GR-24 **3**, a synthetic analogue of the family of strigolactone plant hormones.[1] The methodology was then extended to the first enantioselective synthesis of naturally occurring (+)-5-deoxystrigol **5** and related stereoisomers.[2] In both cases, high ee's and levels of regioselectivity were observed for both cyclobutanones **2** and **4** when C-2 symmetric pyrrolidines were used as chiral auxiliaries (**1**, X = chiral amines).

[1] Lachia M., Jung P. M. J., De Mesmaeker A. *Tetrahedron. Lett.* **2012**, *53*, 4514-4517
[2] Lachia M., Dakas P.-Y., De Mesmaeker A. *Tetrahedron. Lett.* **2014**, *55*, 6577-6581

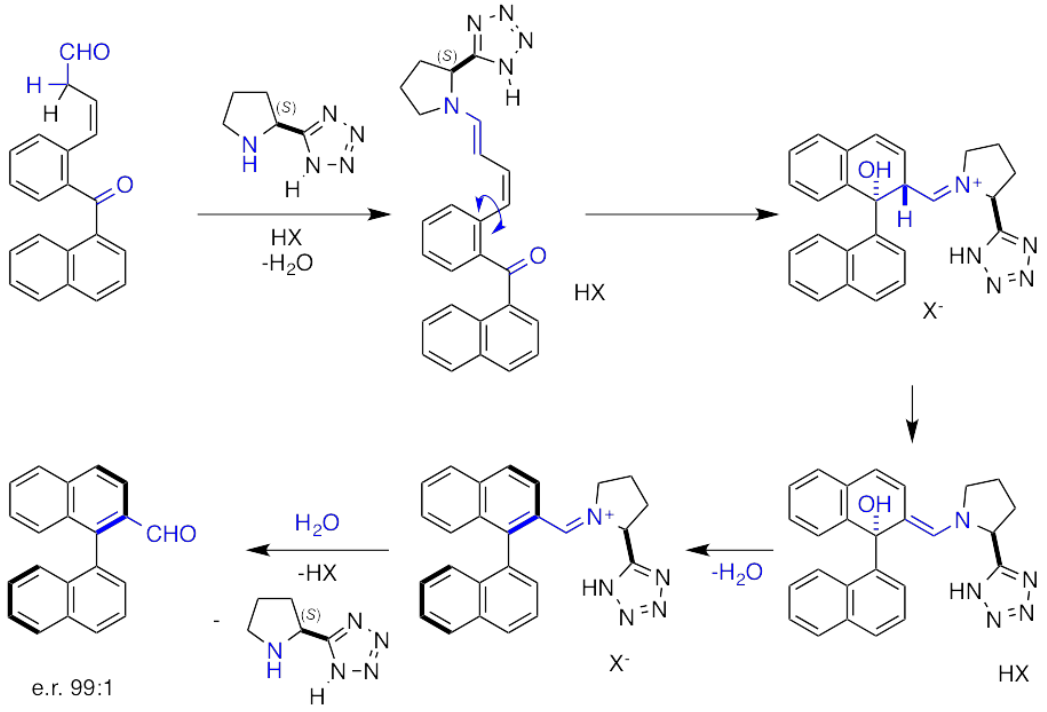
Organocatalytic Atroposelective Aldol Condensation

A. Link[1], C. Sparr[1]*

[1]University of Basel

Axially chiral compounds are important building blocks for various applications, e.g. in ligand design. Despite the importance of atropisomers such as binaphthyl derivatives, only few stereoselective methods are available for their synthesis.

A catalytic method was developed that converts ketoaldehyde precursors into tri-*ortho*-substituted biaryls upon treatment with a pyrrolidinyl-tetrazole catalyst. The stereochemical information is thereby efficiently transferred from the catalyst into the axial chirality of the product. Initially, an activated dienamine is formed to trigger a subsequent cyclization followed by a second α-deprotonation. This activates for a dehydration step leading to the formation of an aromatic ring providing sufficient driving force for the reaction. Hydrolysis to regenerate the catalyst gives the binaphthalene-carbaldehyde with an e.r. = 99:1.



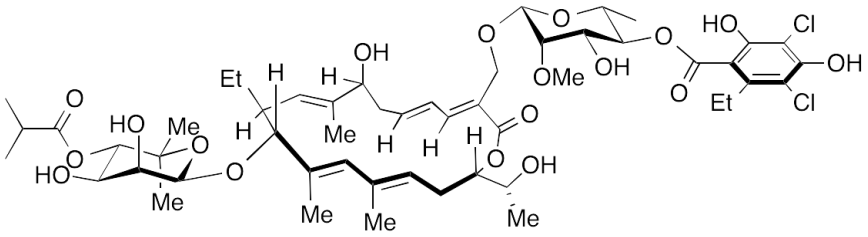
A. Link, C. Sparr, *Angew. Chem.* **2014**, *126*, 5562–5565; *Angew. Chem. Int. Ed.* **2014**, *53*, 5458–5461.

Total Synthesis of Fidaxomicin

E. Kaufmann[1], H. Hattori[1], H. M. Ondozabal[1], K. Gademann[1]*

[1]University of Basel

Fidaxomicin is a FDA-approved narrow spectrum antibiotic and currently used for the treatment of *Clostridium difficile* infections. This macrolide has also been found to exhibit potent biological activity against the multi-drug resistant *Mycobacterium tuberculosis*, however its poor pharmakokinetics prohibit its use as a drug.[1] Surprisingly, in spite of its significant biological properties and unique molecular structure no total synthesis of fidaxomicin has ever been reported since the first isolation in 1975.[2]



fidaxomicin

The total synthesis of this challenging 18-membered macrolide should pave the way to generate structurally diverse analogs and could provide new insights into the structure-activity relationship. After our successfull synthesis of the core aglycone,[3] we will present the first total synthesis of fidaxomicin.

[1] Review: W. Erb, J. Zhu, *Nat. Prod. Rep.* **2013**, *30*, 161-174.
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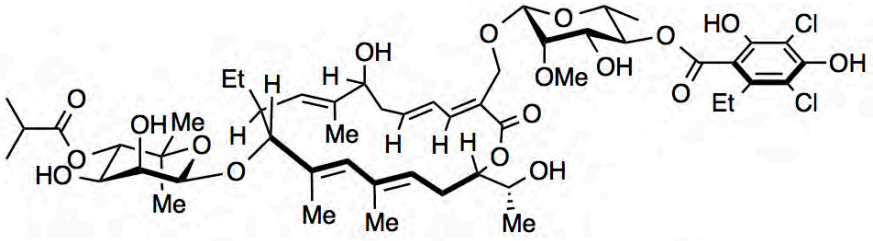
[3] H. Miyatake-Ondozabal, E. Kaufmann, K. Gademann, *Angew. Chem. Int. Ed. Engl*. **2015**, *54*, 1933–1936.

Preparation of Fidaxomicin Analogs via Total Synthesis

H. Hattori[1], E. Kaufmann[1], H. M. Ondozabal[1], K. Gademann[1]*

[1]University of Basel

Fidaxomicin is a new class of antibiotic natural product, which has been recently approved for the clinical treatment of diarrhea-associated infections by the FDA. In addition, this compound has also been found to be effective against multi-drug resistant *Mycobacterium tuberculosis* strains (‹ 0.1 mg/L).[1] Moreover, this promising antibiotic features a synthetically interesting structure, including by two β-linked, unique carbohydrates and a highly unsaturated macrolide with multiple stereogenic centers.



Fidaxomicin (Tiacumicin B, Lipiarmycin A3)

Recently, we accomplished the first, enantioselective total synthesis of fidaxomicin in a highly convergent manner.[2,3] In this context, we will present our investigations towards the synthesis of analogs to clarify the structure activity relationships.

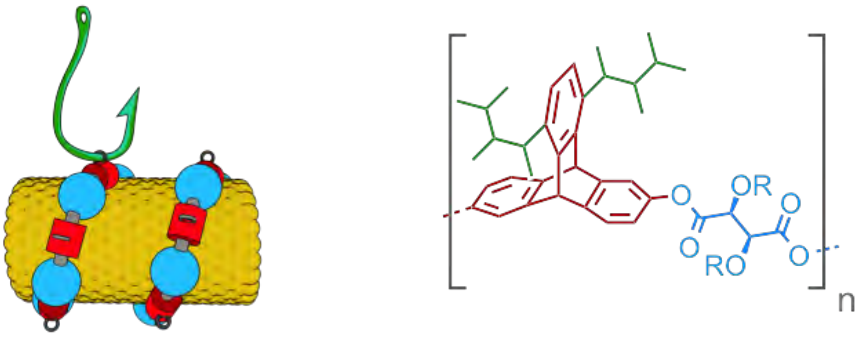
[1] M. Kurabachew, S. H. J. Lu, P. Krastel, E. K. Schmitt, B. L. Suresh, A. Goh, J. E. Knox, N. Ling Ma, J. Jiricek, D. Beer, M. Cynamon, F. Petersen, V. Dartois, T. Keller, T. Dick, V. K. Sambandamurthy, *J. Antimicrob. Chemother.* **2008**, *62*, 713-719.
[2] H. Miyatake-Ondozabal, E. Kaufmann, K. Gademann, *Angew. Chem. Int. Ed*., **2015**, *54*, 1933-1936.
[3] E. Kaufmann, H. Hattori, H. Miyatake-Ondozabal, K. Gademann, manuscript in preparation

Setting the Hook for Specific Single Walled Carbon Nanotubes

I. Bodoky, M. Mayor[1]*

[1]University of Basel

The desire to selectively address SWCNTs with well-defined characteristics such as diameter, n,m-indices and chirality, is an ongoing challenge in today´s research. Although the electronic properties of SWCNTs depend strongly on these characteristics[1]- [4], the selectivity towards traditional means of purification remains low at best. Here, we propose a new strategy to achieve a controlled and selective separation of SWCNTs depending on their size or very likely even their chirality. Conceptually this novel hook consists of an enantiomerically pure building block with a concave π-system, which can synthetically be accessed using Diels-Alder reactions as key steps. Polymerization with interlinking building blocks then leads to chiral ribbons, which are envisaged to coat selectively one type of SWCNT and disperse it. The driving force for the coating process is mainly the interaction of the SWCNT with the concave π-moiety while the size exclusion is defined by the interlinking molecules and the resulting secondary structure of the polymer. Variation of the linkage allows altering of the properties of the polymer at a late stage in the assembly and ultimately defines the dispersion capability of the polymer. As a reliable release of the coated SWCNT is highly desirable, we further present retroDiels-Alder-based uncoating strategies.



Concept picture of a polymer wrapping around a single walled carbon nanotube (left). Molecular scheme of a monomer with proposed dispersing properties (right).

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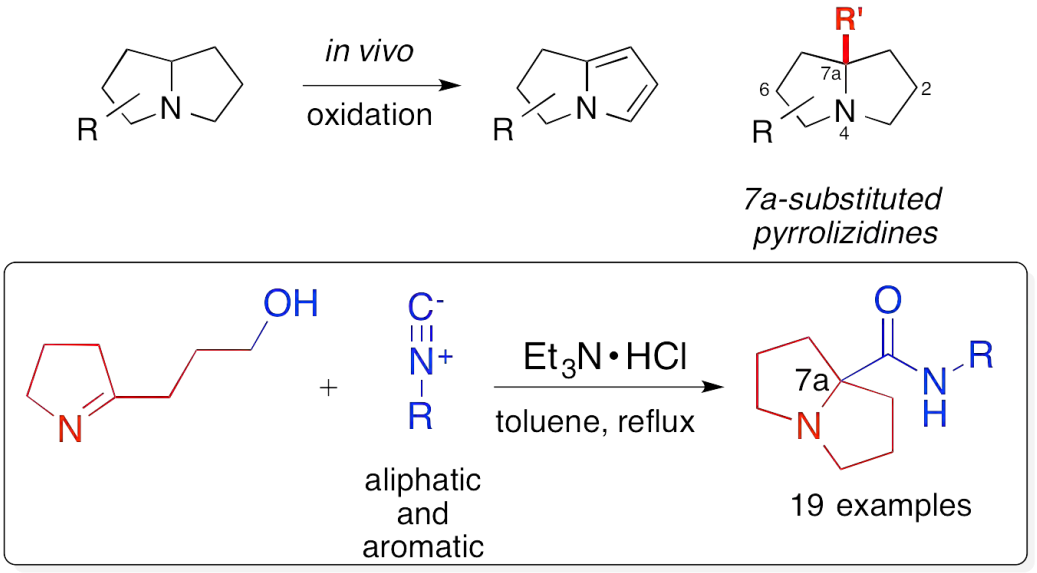
Direct preparation of pyrrolizidines using imines and isonitriles

I. P. Kerschgens[1], K. Gademann[1]*

[1]University of Basel

Pyrrolizidines constitute a privileged ring structure in alkaloids, with hundreds of natural products employing this motif.[1] The utilization of these bicyclic *N*–heterocycles in drug discovery has been hampered by their well-known *in vivo* oxidation to the corresponding pyrrole derivatives, which can undergo undesired off-target reactions.[2] One way of preventing this aromatization involves quaternization by the presence of an additional substituent on the 7a-position. Interestingly, among the many approaches to these heterocycles, there are only few methods reported in the literature to prepare these 7a-substituted pyrrolizidine carboxamides.[3] We describe an acid mediated annulation reaction for the direct preparation of 7a-substituted unnatural pyrrolizidines. A hydroxy-functionalized pyrroline is reacted with a large variety of isonitriles directly resulting in the target compounds. The reaction is operationally simple and tolerates air and water and the resulting pyrrolizidines can be further transformed to the corresponding oxidized and reduced derivatives. Preliminary mechanistic studies were performed to understand this unusual cyclization reaction.



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Chemical modification of peptide and proteins for UV postionization and quantum interference experiments

J. Schaetti[1], U. Sezer[2], L. Mairhofer[2], J. Cotter[2], M. Arndt[2], V. Köhler[1]*, M. Mayor[1]*

[1]University of Basel, [2]University of Vienna

The current world mass record for quantum interference experiments relies on the careful design of the analyte molecules, i.e. chromophores decorated with highly fluorinated tags. [1-4] Quantum interference experiments require slow molecular beams and accordingly postionization of the neutral analyte in the gas phase for mass detection. Thermal evaporation of peptides without decomposition is notoriously difficult due to the thermal lability and strong intermolecular interactions of the analytes.[5] In addition their postionization is hampered by the absence of suitable chromophors, if the peptide sequence displays a low tryptophan content.[6] To investigate postionization of peptides in the gas phase, a range of model compounds were prepared to a) reduce intermolecular interactions and thereby improve volatility and b) introduce suitable ionizable groups. First results on the selective chemical modification of a large peptide for improved detection and a set of smaller model compounds for evaporation studies will be presented.

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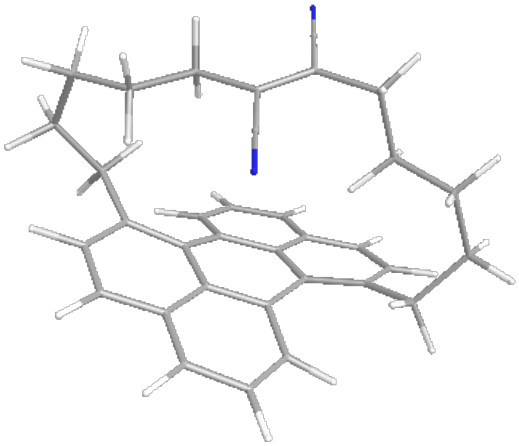
Towards a Perylene-Based Cyclophane with Charge-Transfer Capability

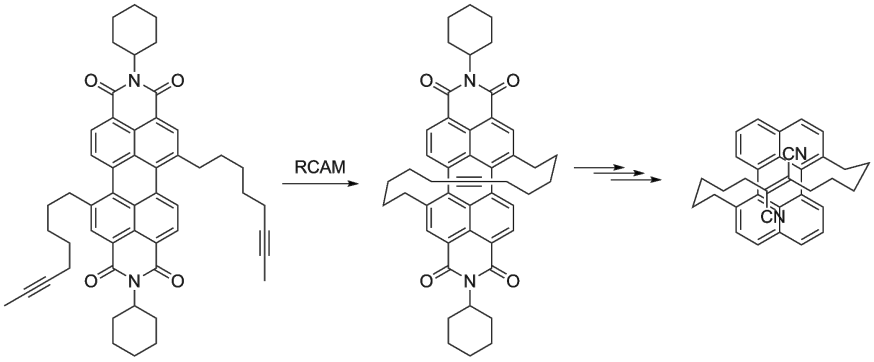
K. Weiland[1], M. Mayor[1]*

[1]University of Basel

Donor-acceptor cyclophanes are desirable molecules for the use in molecular junctions, since they have tuneable electric conductivity upon UV-irradition.[1] A new perylene-based cyclophane will be synthesized containing an electron-accepting fumaric nitril moiety, starting from readily available perylene-3,4,9,10-tetracarboxylic dianhydride.



The key step in the synthesis of the target compound is the ring-closing-alkyne metathesis (RCAM) to give the triple-bond-containing macrocycle.[2] The resulting macrocycle will be further functionalized to give the target donor-acceptor-compound.



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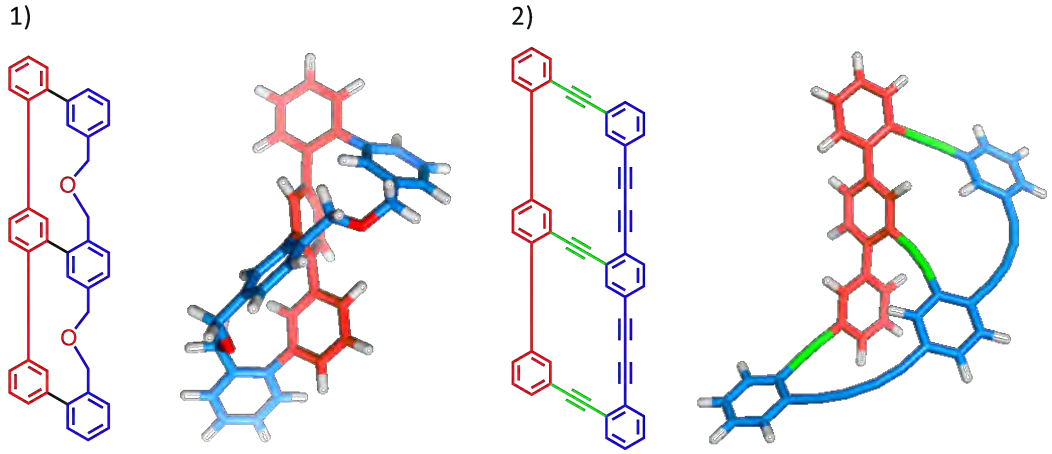
Synthesis of a Diacetylene-Bridged Geländer-Type Oligomer

L. M. Bannwart[1], M. Mayor[1]*

[1]University of Basel

Atropisomers are chiral compounds that do not contain sterogenic centers, but a stereogenic axis. While the synthesis of chiral compounds containing chiral centers has been an important field of research for a long time, little has been known about atropisomeric compounds, which were treated as an “academic curiosity”. The interest in atropisomers started with the discovery that the configuration around the biphenyl axis is an important factor to control the pharmacological properties of bioactive compounds. Combined with their usefulness as catalysts in asymmetric synthesis, biphenyls became prominent and well-studied examples of “chiral compounds without stereogenic center”.



Vögtle *et al* [1] described a new class of bridged terphenyl compounds namely geländer oligomers. In the classical geländer oligomers the optical inactive *meso* form is more stable than the pair of enantiomers. Recently in our group, we reported a novel type of geländer oligomers that cannot exist as a *meso* form. [2] This benzyl ether-bridged molecule (**1**) has, however the lowest barrier of racemisation measured so far. For this reason, we designed a new diacetylene-bridged molecule (**2**), which is expected to be more rigid and, consequently the barrier of the racemisation process in this molecule should be significantly slower. The synthesis towards **2** will be discussed on this poster.

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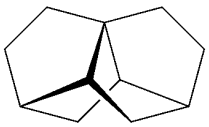
Synthesis of an Unknown Tetracyclic Derivative of Norbornane

L. D. Bizzini[1], M. Mayor[1]*

[1]University of Basel

One of the challenges of synthetic organic chemistry is structural diversity, in particular, at the level of small molecular building blocks.[1] New compounds and compound classes in the size range of small molecules (smaller then 500 g/mol) are of interest since they may display unforeseen properties and lead to new structural motifs.[2] The computer-assisted enumeration of the chemical space addresses this challenge by generating all possible molecules for a give number of atoms (excluding hydrogen) under consideration of specific rules.[3] One particular example found in the chemical universe database (GDB-11) is the yet unknown tetracyclic hydrocarbon **1**. This esthetically pleasing, *C*2-symmetrical, chiral molecule is comprised of three partially superposed norbornyl units. It is surprising that this unstrained molecule has not yet been synthesized in over 100 years of norbornane chemistry.[4] The goal of this project is to synthesize and study the properties of hydrocarbon **1**. Different strategies to build the tetracyclic scaffold will be discussed in the presentation.



1

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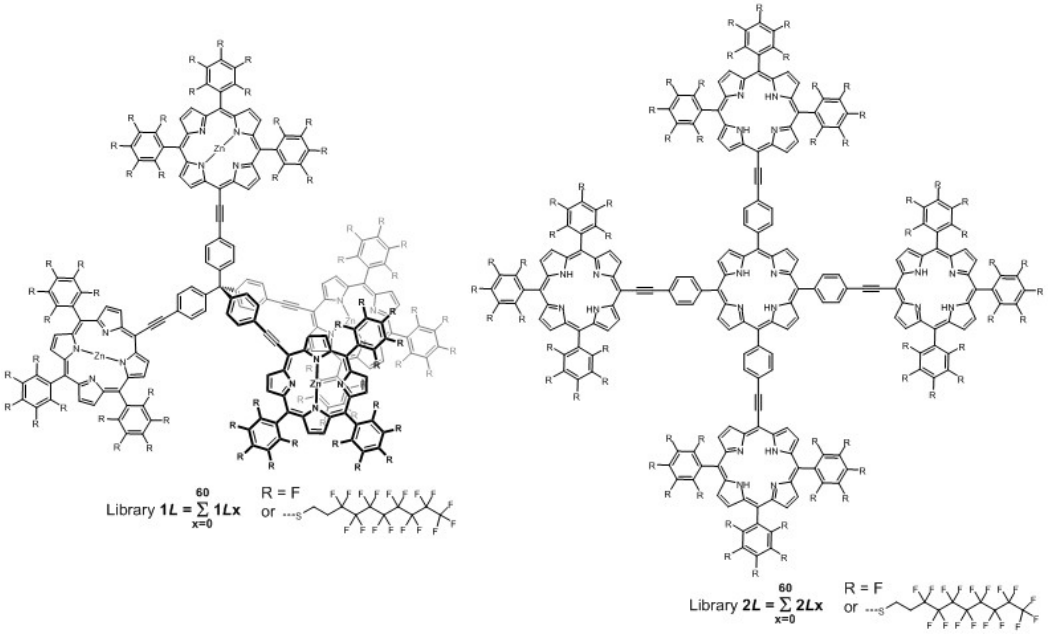
Molecules in Gasphase: Synthesis of Multi-Porphyrin-Systems for Quantum Interference Experiments

L. Felix[1], U. Sezer[2], M. Arndt[2], M. Mayor[1]*

[1]University of Basel, [2]University of Vienna

Matter-wave dualism is a fundamental concept in quantum physics. The observation of wave properties of heavy organic molecules can be used to approach the borderline between classical and quantum physics. Using a porphyrin library we were able to push the mass limit of interfering particles beyond 10'000 amu.[1] Motivated by the prospect to study quantum interference of even higher masses in a novel interferometer we synthesized two libraries based on porphyrin-tetramer (Library **1*Lx***) and on the stronger conjugated pentamer (Library **2*Lx***).[2] Using a modular fourfold Sonogashira cross-coupling we were able to synthesize both multi-porphyrin systems. These libraries should push the mass limit of interfering particles above 20'000 amu. To perform the challenging quantum interference experiments using the novel interferometer photoionization and evaporation studies have been performed.[3]



Scheme 1: *Multi-Porphyrin-Systems (*Library ***1Lx*** *and* Library ***1Lx****).*

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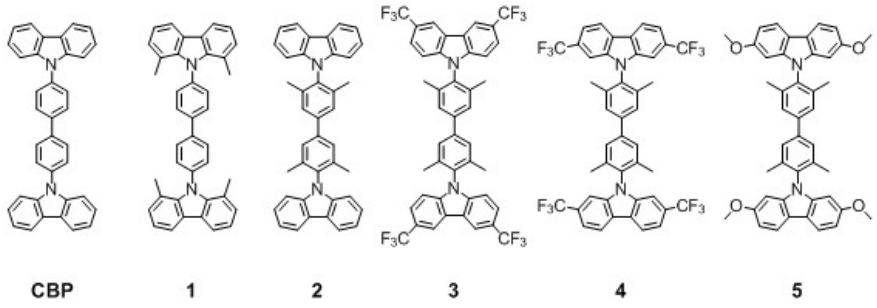
Rotational restricted and functionalized CBP derivatives for blue emitting OLEDs

M. Hellstern[1], M. Gantenbein[1], M. Mayor[1]*

[1]University of Basel

Used as building blocks for organic light emitting diodes (OLED), 4,4'-dicarbazole-1,1'-biphenyl (CBP) derivatives are of major interest in the field of electrophosphorescence.[1] Carbazole building blocks in CBP provide a high triplet energy state and thereby enable the use as matrix materials with an efficient energy transfer to a phosphorescence light emitting dye.[2] For an efficient energy transfer especially for deep blue light emitting dyes, the triplet energy state of the matrix material should be as high as possible.

Five new derivatives were synthesized by introducing sterically demanding substituents to the carbazole subunit in 2,7 position for compound **1** and to the biphenyl backbone in compounds **2**-**5**. With this modification we achieved a perpendicular alignment between the carbazole subunit and the biphenyl backbone, resulting in a decreased π-conjugation through the molecule and therefore an increased triplet state energy. Furthermore by introducing electron withdrawing and electron donating groups at the carbazole subunit, a shift of the HOMO / LUMO level was achieved.[3]



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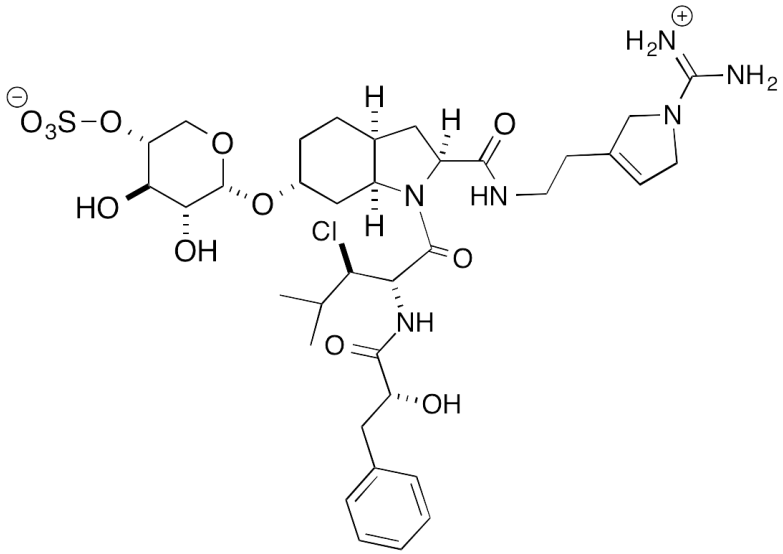
Total synthesis of Aeruginosin828A

M. Scherer[1], D. Bezold[1], V. Grundler[1], K. Gademann[1]*

[1]University of Basel

Aeruginosins constitute a family of linear modified peptides naturally occurring in cyanobacterial waterblooms. Today, over 50 compounds of this class of natural products are known.[1] Aeruginosin 828A was isolated form *Planktothrix rubescens* and it has been shown strong inhibition of thrombin and trypsin. Furthermore, aeruginosin 828A was found to be a potent biotoxin.[2]



Aeruginosin 828A

The aim of this project is to confirm the proposed structure by total synthesis. The effect of the chlorine and the sulfate residues on the biological activity should be clarified through analogue syntheses.

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Radical Cyclizations involving Aryl Azides as Radical Traps

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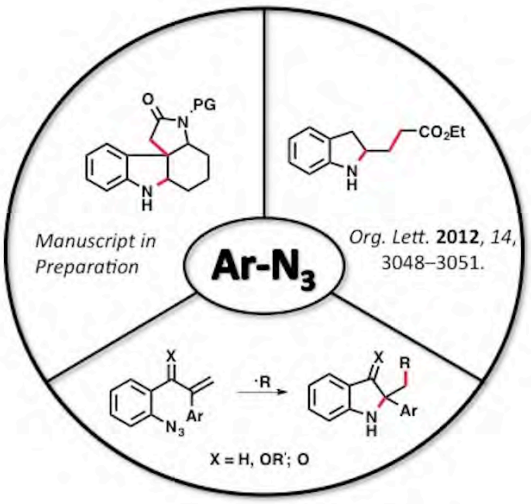
[1]Universität Bern

The formation of carbon–nitrogen bonds using organic azides as radical traps has attracted the attention of many different research groups. We recently described a simple approach to prepare indolines and benzopyrrolizidinones [1] as well as the tetracyclic core of *Aspidosperma* Alkaloids [2] *via* a radical cascade involving aryl azides as radical traps. As a third example we are developing a model reaction which could be used as a route to another class of indole alkaloids such as Hinckdentine A.[3]



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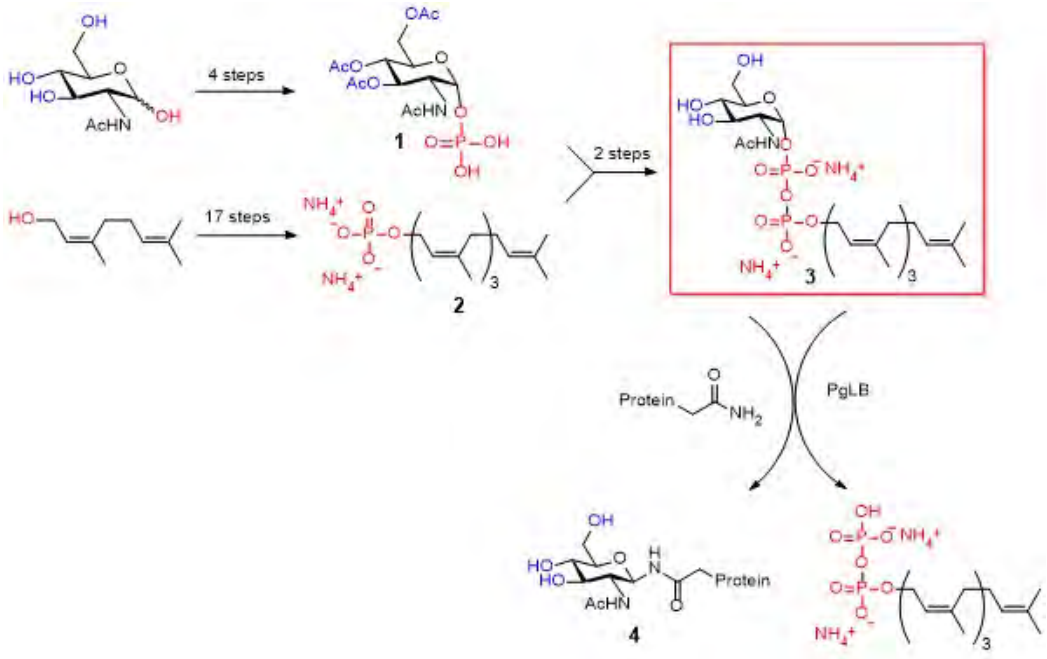
Lipid Linked Oligosaccharide (LLO) Analogues as Bacterial Oligosaccharyltransferase (OST) PgLB Substrates

J. Boilevin[1], K. Locher[2], T. Darbre[1], J.-L. Reymond[1]*

[1]University of Bern, [2]ETH Zürich

N-linked protein glycosylation is an essential post-translational modification that links glycans from a lipid carrier to the asparagine residues of polypeptide chains. PgLB, the bacterial OST responsible for this glycosylation, is a well known example of this complex system[1]. The crystal structure of *Campylobacter Lari* PgLB was recently reported[2], leading to a revision of the proposed mechanism. In relation with structural studies, we recently showed Structure Activity Relationship (SAR) on the polypeptide chain that led to further insight into the reaction mechanism and factors affecting substrate binding and enzyme turnover[3].
Our aim is to perform similar SAR studies with respect to the LLO substrates. Toward this goal, we have established a synthesis of LLO analogues following an established route[4],[5].The synthesis was optimized for efficiency by revising several key steps, enabling the preparation of a broad family of LLO analogues.



Scheme 1: Synthetic pathway of an example of LLO analogue synthesis and glycosylation step

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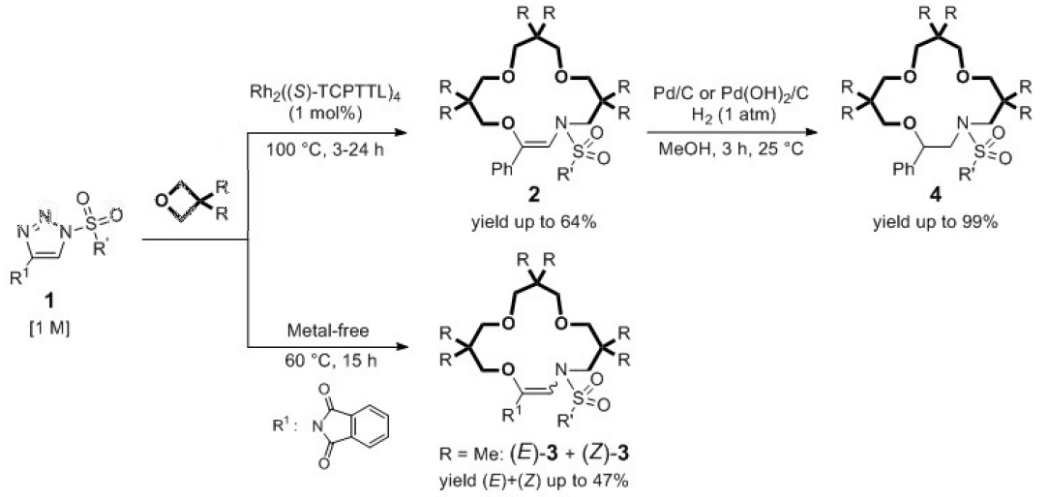
Synthesis of Nitrogen-Containing Macrocycles via α-Imino Diazo Intermediates

A. Guarnieri Ibáñez[1], F. Medina[1], C. Besnard[1], L. Guénée[1], J. Lacour[1]*

[1]University of Geneva

N-sulfonyl-1,2,3-triazoles are known to decompose under thermal and/or metal catalyzed reaction conditions leading to electrophilic *α*-imino carbenes.[1] These intermediates undergo many interesting and original processes, from cyclopropanations[2] to ylide forming reactions and subsequent transformations, such as small[3] and mid-size ring synthesis.[4]

Recently, our group has developed an interesting Rh (II) catalyzed macrocyclization reaction between oxetane and α-diazo-β-ketoesters leading to 15-membered crown ethers.5 Herein we expand this report with a variety of nitrogen-containing macrocycles starting from *N*-sulfonyl-1,2,3-triazoles (**1**) and oxetanes. Three oxetanes and one electrophilic *α*-imino carbene condense in a one pot process (1M) leading to the macrocycles of type **2** (33-64%). With *N*-sulfonyl-4-phthalimidotriazoles, metal-free conditions are possible.6 In presence of oxetane, analogous macrocycles (**3**) are generated but surprisingly, mixtures of *E* and *Z* isomers were formed. Importantly, despite the steric crowding and a disfavored electronic character, the double bond can be hydrogenated leading to compounds of type **4**.



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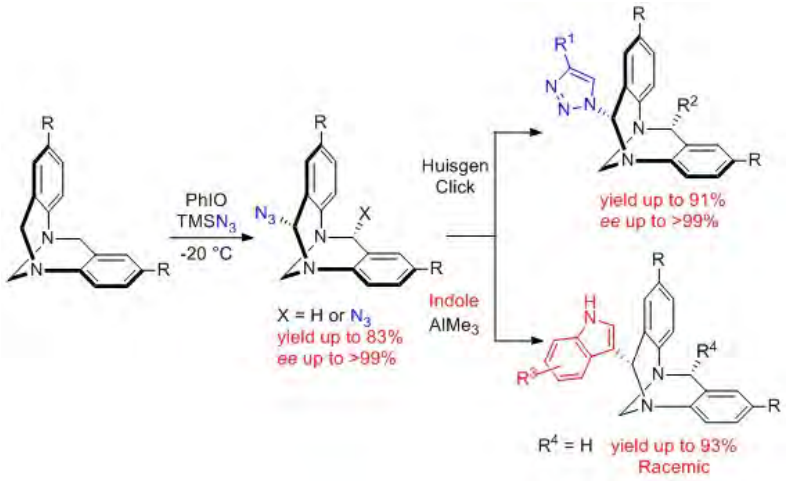
Enantiospecific C-H Azidation and ensuing functionalization of Tröger Bases

A. Bosmani[1], S. Pujari[1], L. Guénée[1], J. Lacour[1]*

[1]University of Geneva

Tröger bases[1] are original bicyclic heterocycles with stereogenic nitrogen atoms that have generated a great interest among the synthetic community due to their potential applications in catalysis, pharmaceuticals and polymer building blocks.[2] Several efforts have been pursued to introduce functional groups at the a positions of the stereogenic tertiary nitrogen atoms.[3] Herein, to exploit the extended versatility of the azide functional group, we report a regio- and stereoselective sp^3 C-H azidation of Tröger bases. Introduction of either one or two azido groups is afforded at benzylic positions in one step under mild conditions, with high enantiospecificity (*ee* up to ›99%) and in moderate to good yields (up to 83%) using hypervalent iodine chemistry ($PhIO/TMSN_3$).



Interestingly, nucleophilic substitution of the azide group by indoles is afforded in an apparent violation of the Bredt's rule. Also, a large family of mono- and bistriazoles can be afforded.

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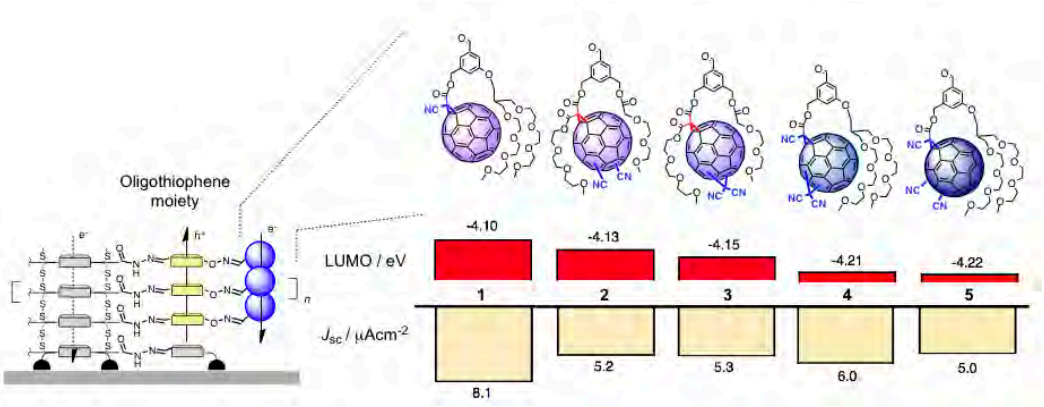
A Series of Novel Redox Gradient Fullerenes in Triple-Channel Photosystems

A. Bolag[1], J. Lopez-Andárias[2], C. Nancoz[1], E. Vauthey[1], C. Atienza[2], N. Sakai[1], S. Matile[1]*, N. Martín[2]*

[1]School of Chemistry and Biochemistry, University of Geneva, Switzerland, [2]Departamento de Química Orgánica, Universidad Complutense, Madrid, Spain

In current materials sciences, it is desirable to build organic materials for structures of comparable complexity to natural ones with similar function. Our research focuses on exploring synthetic methods to build complex architectures of artificial photosystems directly on solid surfaces. In our previous work, we have developed four redox gradient C60 fullerene derivatives for ordered/oriented self-organizing surface- initiated polymerization (SOSIP) with templated stack exchange (TSE) strategy [1]. In order to understand properties of further π-acidic fullerenes, we have synthesized five novel, structurally similar fullerenes with lower redox potential and investigated their compatibility with triple-channel SOSIP-TSE architectures [2].



The most electron-deficient fullerene **5** gave a remarkably low LUMO energy of -4.22 eV. However, the highest photocurrent activity of 8.1 μA/cm^2 was found with the best-preserved π-system of the monodisperse fullerene **1**. All the mixtures of regioisomers showed weaker activities. However, the decreasing LUMO energy is helpful for improving activity if we compare the redox potentials of these fullerenes with our previous more π-basic fullerenes.

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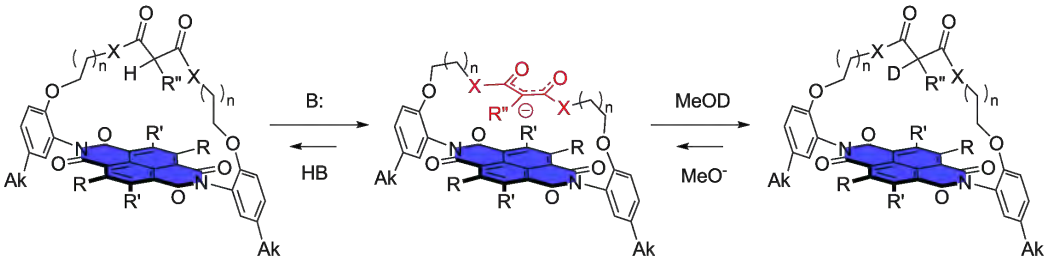
The Anion-π Interaction: A Tuneable Non-Covalent Interaction for Catalysis

F. N. Miros[1], Y. Cotelle[1], S. Benz[1], Z. Yingjie[1], N. Sakai[1], S. Matile[1]*

[1]University of Geneva

Applications of the anion-π interaction, an underrated non-covalent bond between an anion and an electron-deficient arene originally discovered by computational methods, remain virtually inexistent. However, it has been shown to make anion transport across membranes possible [1]. More recently, anion-π interactions have been explored with the same naphthalenediimides (NDI's) to accelerate several reactions with an anionic transition states [2,3].



To confirm enolate intermediate stabilization by anion-π interactions, a deuterium exchange protocol has been developed. Macrocycles comprising NDI's of varied core substitution, leading to varied π-acidity, and covalently linked malonate are observed through ^{1}H NMR spectroscopy. The obtained deuterium exchange rates are then compared with a variety of free diethyl malonate derivatives to determine relative transition-state stabilization energies ($\Delta\Delta G_{TS}$), ground-state stabilization energies ($\Delta\Delta G_{GS}$), and pK_a's [4]. Stabilization energies of up to 20 kJ/mol and decreases in nearly six pK_a units were observed for the most π-acidic NDI malonates. These increases in malonate acidity are due to an improved stabilization of enolates by stronger anion-π interactions.

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Twisted Push-Pull Fluorophores as Mechanosensitive Probes

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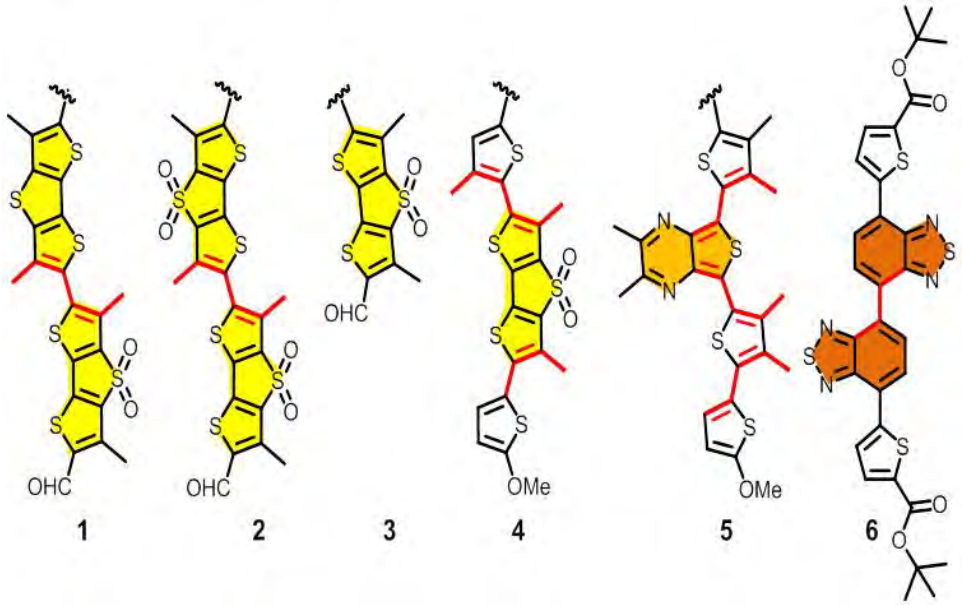
[1]University of Geneva

Fluorescent probes are a main tool for the study of cellular membrane properties such as fluidity, lateral pressure or polarity.Thus our group proposed novel amphiphilic oligothiophene push-pull systems, in which planarization and polarization of the oligothiophene core is induced by environmental changes, enabling the sensing of membrane fluidity, homogeneity and hopefully tension.[1] The sensitivity of these mechanophores toward their environment arises from the planarization of the twisted oligothiophene scaffold upon their passage to a more confined environment.[2]

In the new generation of molecular flippers the quantum yield and mechanosensitivity toward membrane fluidity were improved by the introduction of dithienothiophene S,S-dioxides. The planarization of the molecular flipper **1** in liquid-ordered (Lo) and solid-ordered (So) membranes results in red shifts in excitation of up to +80 nm, indicating that the probe can detect in membrane bilayers with excellent quantum yields above 80% and lifetimes above 4 ns.[3] Furthermore, a series of dithienothiophene S,S-dioxide (**2-4**) as well as thieno[3,4]pyrazine (**5**) and 2,1,3-benzothiadiazole (**6**) flippers were synthesized.[4] A comparison between different flippers supports that dithienothiophene S,S-dioxides are the best and two different flippers are needed to really swim (**1**). Current efforts focus on increasing the dipole moment of the twisted push-pull mechanophores. This is of interest to increase mechanosensitivity and possibly also sense membrane potential.



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Arylamine Tribenzopentaphenes: Versatile Synthesis and study of their Hole Mobility

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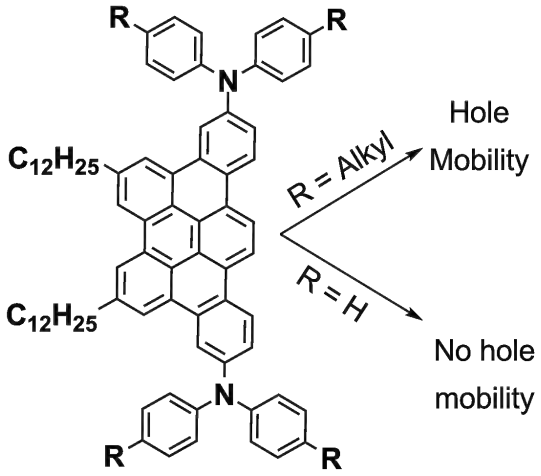
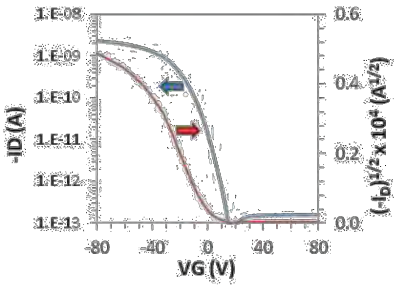
[1]Gulf University for Science & Technology, Kuwait, [2]Science and Engineering Department, University of Washington, Seattle, USA, [3]University of Fribourg, Switzerland

We report the versatile synthesis of two tribenzo[fj,ij,rst]pentaphene (TBP) derivatives bearing two diarylamine substituents attached at the opposite ends of the aromatic core. Field effect transistor (FET) devices of the bis-diarylamine-TBP compounds were fabricated using spin coating under different concentration, spin speed, and solvent conditions. Emission spectra and surface investigation by atomic force microscopy (AFM) reveal the formation of aggregates induced by the strong π-π stacking of the aromatic core leading to island features, and thus, unexpected low hole mobilities. The synthetic strategy we show herein, however, offers the possibility to decorate the TBP core structure with various charge carrier peripheral groups and optimized alkyl chains, which should improve the crystalline property of their thin films upon deposition, leading consequently, to a better hole transport mobility.





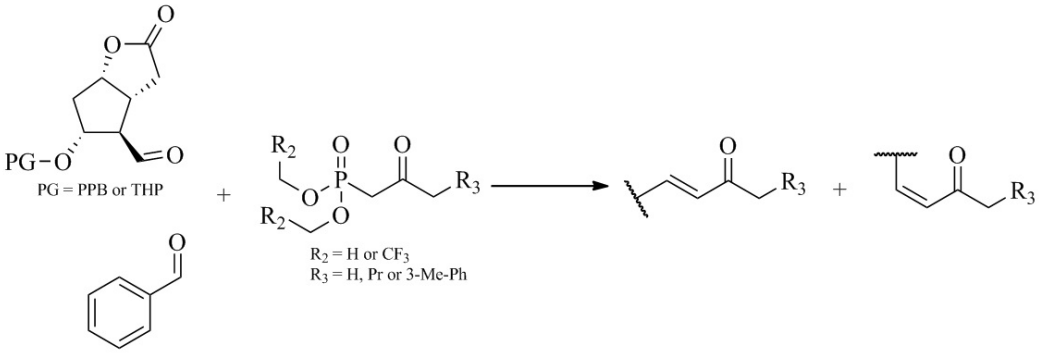
Route to the controlled formation of prostaglandin double bonds

K. Molnar[1,2], L. Takács[1], Z. Kardos[1], F. Faigl[2]

[1]Sanofi - Chinoin, [2]Budapest University of Technology and Economics

Our company is a world-leader in the manufacture of prostaglandin API-s. It is well known that prostaglandins contain *cis* or *trans* double bonds in their side-chains. To achieve successful marketing we are expected to synthesize not only API-s but also their isomeric impurities.

Dimethyl 2-oxophosphonates are widely used reagents in Horner-Wadsworth-Emmons reaction for the selective preparation of *trans* double bonds of (*E*)-*α,β*-unsaturated esters or ketones. However, it has been reported[1,2] that bis(2,2,2-trifluoroethyl)-2-oxophosphonates can promote the formation of *cis* double bonds in these compounds. This modification in the structure of 2-oxoalkylphosphonates provides the possibility to synthesize prostaglandins or other unsaturated compounds with *cis* and/or *trans* double bonds on request. These results inspired us to explore the scope and limitations of HWE-reactions with 2,2,2-trifluoroethyl-group-bearing phosphonoesters.



This presentation will discuss new preparation methods of bis(2,2,2-trifluoroethyl)[3,4] and 2,2,2-trifluoroethyl methyl 2-oxoalkylphosphonates,[5]among which a number of new trifluoroethyl compounds are to be found. Synthesized phosphonoesters were reacted with different aldehydes in HWE-reactions (Figure 1). It was found that the geometry of the forming double bond was significantly determined by the ester substituents of phosphonates. Reaction conditions influenced the Z/E selectivity in the case of 2,2,2-trifluoroethyl methyl and bis(2,2,2-trifluoroethyl) 2-oxoalkylphosphonates. The chemical structure of aldehydes also highly affected the isomeric ratio.

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Towards a Total Synthesis of Fijiolide A

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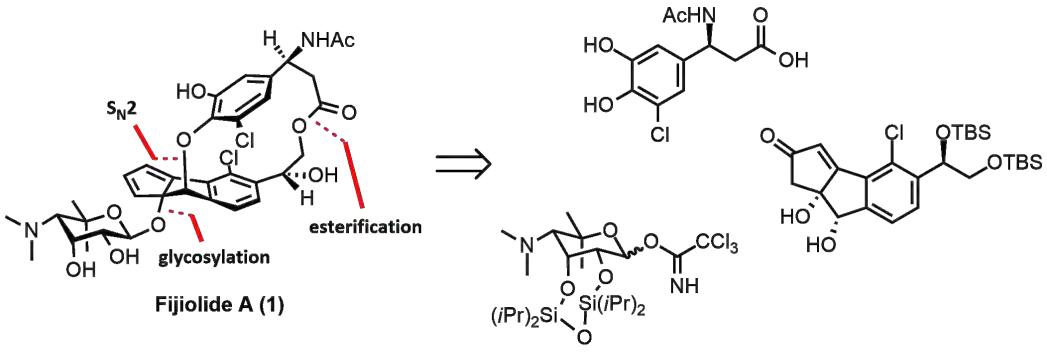
[1]EPF Lausanne

In 2010 *Fenical et al.* reported the isolation of Fijiolide A (**1**) from a marine-derived actinomycete of the genus *Nocardiosis*.[1] The chloroaromatic natural product was shown to exhibit remarkable biological activity by reducing the TNF-α-induced NFκB activation by 70% with an IC_{50} value of 0.57μM. As an inducible transcription factor, NFκB regulates the expression of more than 400 different genes. Many of whom encode tumorgenesis relevant proteins, e.g. cyclooxygenase (COX)-2 or matrix metalloproteinase (MMP)-9.[1]
Apart from the pharmacological potential, Fijiolide A engages particular attention due to its highly complex molecular structure. Thus, **1** consists of a chlorocyclopenta[α]indene carbon framework which forms a constrained macrocycle with an attached β-tyrosine moiety. This 16-membered macrolactone acts as the aglycon of an amino-ribopyranose unit. Ultimately, Fijiolide A exhibits atropisomerism arising from hindered rotation of the β-tyrosine within the macrocycle.
1 possesses close structural resemblance with the aromatization products of numerous potent enediyne antitumor antibiotics, especially the C-1027 chromophore.[2] However, Fijiolide A is unique, since it is the sole Masamune-Bergman cyclization product displaying notable biological activity.[2,3]

We disclose our advanced synthetic progress towards Fijiolide A, along with an accomplished synthesis of the Fijiolide A aglycon via an atroposelective macrocyclization approach.



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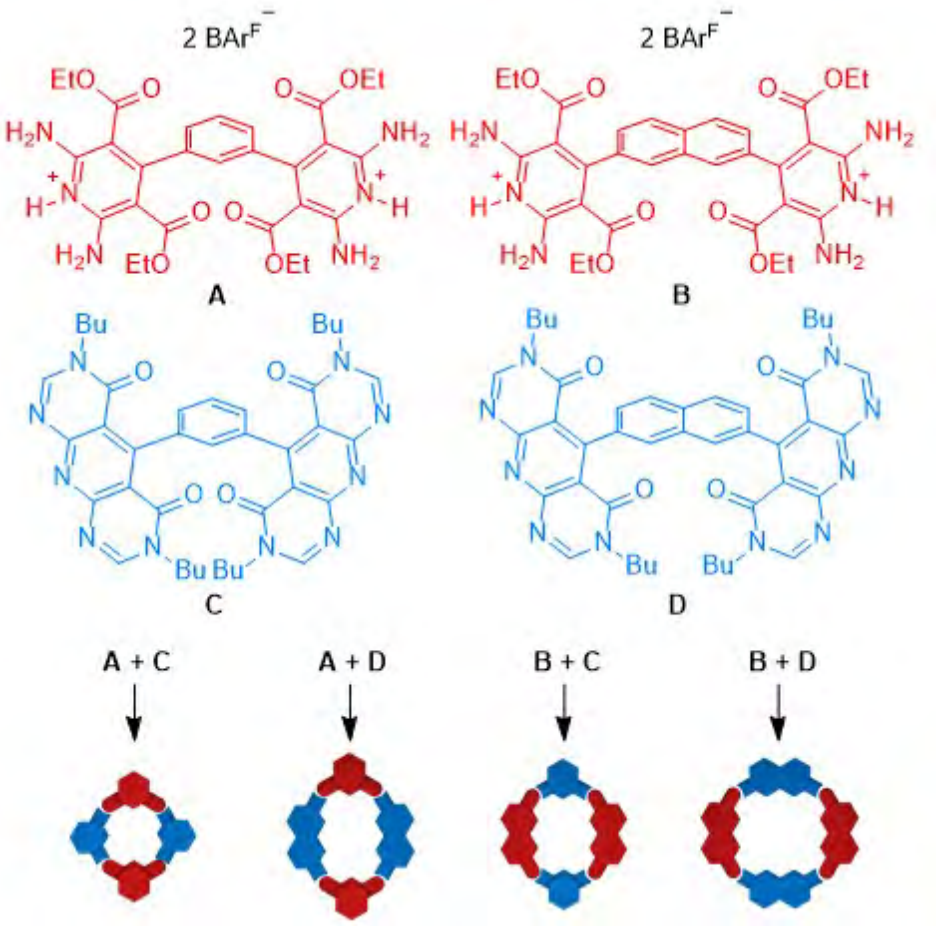
Molecular and Polymeric Nanostructures Based on a Novel AAA-DDD Triple Hydrogen Bonding Motif

M. Papmeyer[1], K. Severin[1]*

[1]EPF Lausanne

The development and implementation of contiguous multipoint hydrogen bonding motifs in molecular scaffolds holds great promise for the design of new materials and the controlled assembly of complex supramolecular architectures. So far, the synthesis of AAA-acceptor and DDD-donor molecules has been cumbersome and AAA-DDD-type motifs have hardly been used for structural supramolecular chemistry. In order to overcome this limitation, we developed facile and flexible method for the synthesis of a new AAA-DDD triple hydrogen bonding motif. The method allows accessing polytopic supramolecular building blocks with precisely oriented AAA and DDD groups in few steps. These building blocks have been used for the assembly of large macrocycles featuring four AAA-DDD interactions. Furthermore, we demonstrate that the motif can be used for the formation of a semi-rigid supramolecular polymer. An extensive molecular dynamics simulation aides the understanding of the assembly proceess and allowed the determination of the Gibbs free energy of formation for different theoretically possible aggregates.



Revisiting the Suzuki Coupling Based on Volcano Plots and Linear Scaling Relations

M. Busch[1], M. Wodrich[2], C. Corminboeuf[2]*

[1]EPF Lausanne and National Center for Computational Design and Discovery of Novel Materials (MARVEL), [2]EPF Lausanne

Transition metal catalyzed C-C cross couplings such as the Suzuki reaction are central to modern organic chemistry. Computations targeting this reaction are often aimed at exploring the detailed mechanism of key reaction steps and associated activation barriers[1]. While this indeed allowed for significant insights it lacks the predictive power required for the development of new catalysts. This is contrasted by computations performed in surface chemistry. Here detailed reaction steps are often neglected thus, trading accuracy for the possibility to screen a large number of systems efficiently. From these screenings it has been realized that the intermediates' relative stability are not independent but can be described by a set of linear equations[2]. These linear scaling relations can be used for a qualitative analysis of the thermodynamic limitations associated with a reaction[2,3]. A possibility to analyze and compare the activity of individual candidate catalysts offer volcano plots. Volcanoes are constructed based on Sabatier's principle which assumes that an ideal catalyst binds the intermediates such that the binding of the reactants to the catalytic site and the release of the products are balanced (**II** in Fig. 1). When moving away from this optimum the activity is either dominated by the release of the product (**I** in Fig. 1) or the binding of the reactant to the catalytic site (**III** in Fig. 1).

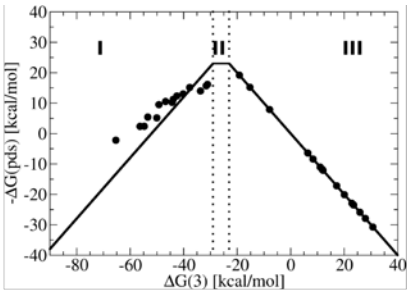


Figure 1: A typical volcano obtained for the Suzuki reaction is shown. The solid lines are derived from linear scaling relations while the dots are obtained from explicit DFT calculations.

Despite the high predictive power and the simplicity of the underlying concepts volcanoes and scaling relations are still restricted to surface chemistry. In the present work a possibility to transfer these concepts to the field of homogeneous catalysis will be shown for the Suzuki reaction. In the first step the existence of linear scaling relations will be tested. Based on these linear scaling relations simulated volcanoes are constructed and used to explore the thermodynamic limitations associated with the Suzuki coupling. A comparison with explicitly calculated results will be made. Employing linear scaling relations and volcano plots the influence of the base, which is a central component for a successful Suzuki coupling, will be explored. A transfer of these concepts to other important organic reactions is planned.

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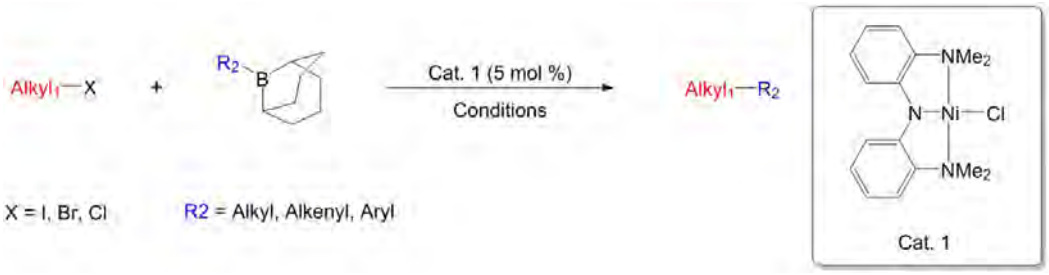
Suzuki-Miyaura Cross-Coupling Reactions of Unactivated Alkyl Halides Catalyzed by a Nickel Pincer Complex

T. Di Franco[1], X. Hu[1]*

[1]EPF Lausanne

While cross-coupling reactions have become a major method for C-C bond formation,[1] it remains challenging to perform the cross-coupling of organometallic nucleophile with unactivated alkyl electrophiles. The difficulty can be partially attributed to the tendency of metal alkyl intermediates to undergo unproductive β-hydride elimination.[2] Our group has developed a well-defined amidobis(amine) Nickel(II) complex, [($^{Me}N_2N$)Ni-Cl] (Cat. **1**, Fig. 1), which is an efficient catalyst for the Kumada-Corriu-Tamao cross-coupling,[3] the C-H functionalization reactions[4] and the Suzuki-Miyaura coupling[5] involving unactivated alkyl electrophiles.



This presentation will show the last results of the investigation into the reactivity of **1** as the catalyst in the Suzuki-Miyaura reaction. The catalyst **1** allows the first Ni-catalyzed Suzuki-Miyaura coupling of alkyl halides with alkenyl-(9-BBN) reagents. The method tolerate various functional groups such as amide, pyrrole, ester, ether, nitrile, acetal and Boc-group. Both primary and secondary alkyl halides including alkyl chlorides can be coupled. The coupling method can be combined with hydroboration of terminal alkynes in *one-pot*, allowing the expedited synthesis of functionalized alkyl alkenes from readily available alkynes with complete (*E*)-selective reaction.

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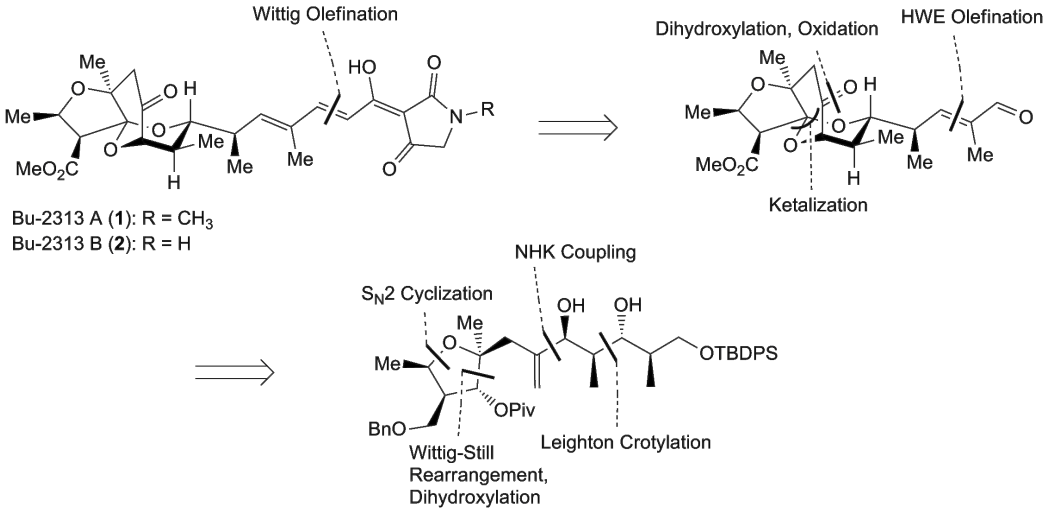
Towards the Total Synthesis of the 3-Acyltetramic Acid Antibiotics Bu-2313A/B

C. Bomio[1], K.-H. Altmann[1]*

[1]ETH Zurich

Pathogens that are resistant to multiple antibiotics are emerging constantly and are a severe threat to public health. Therefore the development of new chemical entities with antibacterial activity is of great importance.[1] Bu-2313 A (**1**) and B (**2**) are highly potent, broad spectrum antibiotics that were isolated in 1979 by Kawaguchi[2] from the oligosporic *actinomycete* strain No. E864-61 and that are members of the acyltetramic acid class of natural products.



In light of their potent biological activity we have embarked on the total synthesis of Bu-2313 A/B (**1**/**2**), based on the retrosynthesis depicted above. We have currently achieved the synthesis of an advanced intermediate as precursor of the challenging tricyclic core structure. In this contribution, the details of the synthesis of this intermediate and further progress towards the total synthesis of the natural products will be presented.

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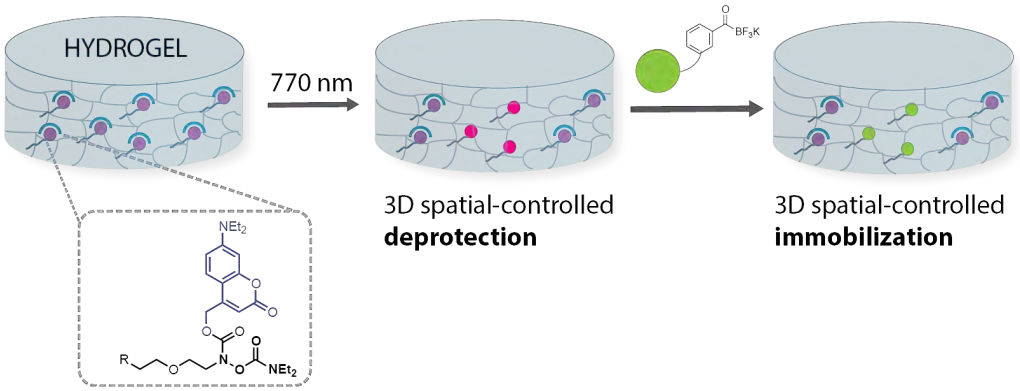
KAT ligation for 3D control in hydrogels using 2-photon microscopy

D. Mazunin[1], N. Broguiere[1], M. Zenobi-Wong[1]*, J. W. Bode[1]*

[1]ETH Zurich

Potassium acyl trifluoroborate (KAT) ligation was exploit for a 3D spatial-controlled modification of hydrogel using two-photon microscopy. *O*-carbomoyl hydroxylamine was protected with a light-sensitive diethylamino coumarin (DEAC) group and incorporated via linker into a hydrogel. Using a two-photon laser, upon exposure to 770 nm, light-caged *O*-carbomoyl hydroxylamine can be selectively deprotected and functionalized chemoselectively in spatial-controlled way.

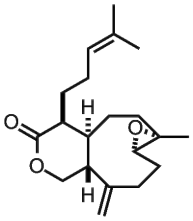


Towards the Total Synthesis of Acalycixeniolide F

L. Betschart[1], K.-H. Altmann[1]*

[1]ETH Zurich

Cancer is one of the major causes of death worldwide. Despite large progress in the field, there is a great need for new medications. Since many secondary metabolites of marine origin are able to kill human cancer cells, they represent valuable lead structures and biological probes for anticancer drug discovery and cancer research in general.[1]

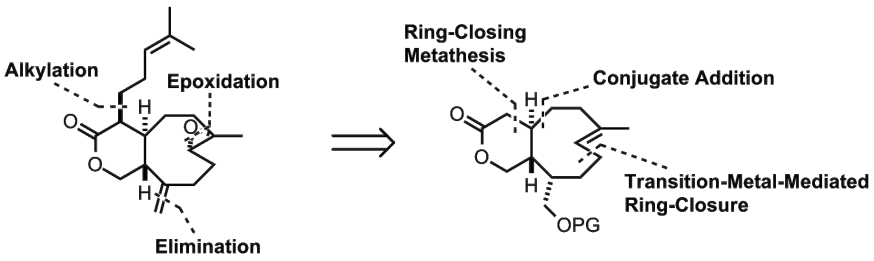


Acalycixeniolide F

Acalycixeniolide F is a diterpenoid of the xenicane class that has been isolated from the soft coral *Acanthogorgia inermis* Hedlund. The compound was demonstrated to inhibit the proliferation of K562 human leukemia cells with an LC_{50} value of 0.2 µg/mL.[2,3]

In order to enable a broader biological evaluation of the compound, we have embarked on the total synthesis of acalycixeniolide F, based on the retrosynthesic analysis outlined below. After biological reevaluation, structure activity relationship (SAR) studies will be carried out with a number of modified analogs.

At this point, we have achieved the synthesis of the 11-oxa-bicylco[7.4.0]tridecane core structure. This presentation will discuss the details of the synthesis of this advanced intermediate and some of the challenges encountered along the way. Further progress towards the natural product will also be presented.



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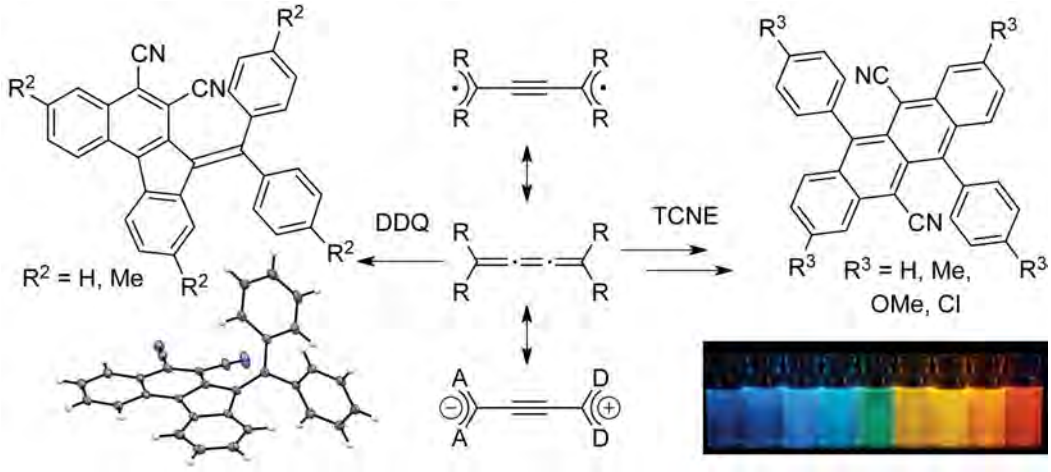
Functional Cumulene-Based Molecular Materials

P. Gawel[1], F. Diederich[1]*

[1]ETH Zurich

The central double bond in [3]cumulenes exhibits triple bond character, both in its length and reactivity. These similarities result from the identical *sp*-hybridization of carbon atoms composing them. We provide comprehensive support for the proacetylenic structure and reactivity of [3]cumulenes both by experimental and theoretical studies. An influence of molecular polarization on this phenomenon was proven by the decrease of the rotational barrier around the cumulene axis and increase of bond length alternation, both of which have been supported by extensive computational studies.

The proacetylenic reactivity of [3]cumulenes is highly dependent on the polarity of the starting material. While in the reaction with TCNE the highly polarized push–pull [3]cumulenes give stable zwitterions,[1,2] the symmetric tetraaryl[3]cumulenes yield, after the reaction cascade, 6,12-dicyano-5,11-diphenyl-tetracenes, which are efficient fluorophores and undergo singlet fission with high yields.[3,4] Additionally, the non-proacetylenic reactivity of tetraaryl[3]cumulenes with DDQ is shown.



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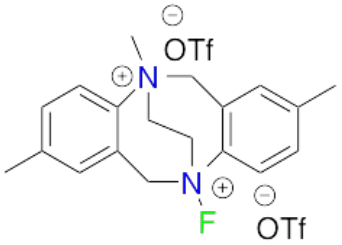
Synthesis, Characterization and Application of an Ethano-Tröger's Base Derived Electrophilic Fluorinating Reagent

R. Pereira[1,2], J. Cvengros[1], V. Gouverneur[2]*

[1]ETH Zurich, [2]University of Oxford

Fluorinated organic molecules play an integral role in pharmaceuticals,1 agrochemicals2 and PET tracers3. The development of mild, user-friendly N–F electrophilic fluorinating reagents such as (*N*-fluoropyridinium salts, *N*–fluorobis(phenyl)sulfonimide (NFSI) and 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo- [2.2.2]octane bis(tetrafluoroborate) (Selectfluor or F-TEDA-BF4)) have made a significant impact on the field of electrophilic fluorination.4As an extension to our research on the development of fluorinating reagents5 and Tröger's base chemistry,6 we would like to report here the synthesis, characterization and application of a novel electrophilic fluorinating reagent **1** based on an ethano-Tröger's base (2,8-dimethyl-6*H*,12*H*-5,11-ethanodibenzo[*b*,*f*][1,5]diazocine) scaffold.



1

The ^{19}F NMR of **1** (N–F) has a chemical shift of (δ) +103 ppm which is unprecedented to the best of our knowledge for an N–F type of reagent. The high chemical shift suggests a higher reactivity profile in comparison to other N–F reagents. Currently we are working towards assessing the reactivity profile as well as developing analogues of **1** as fluorinating reagents.

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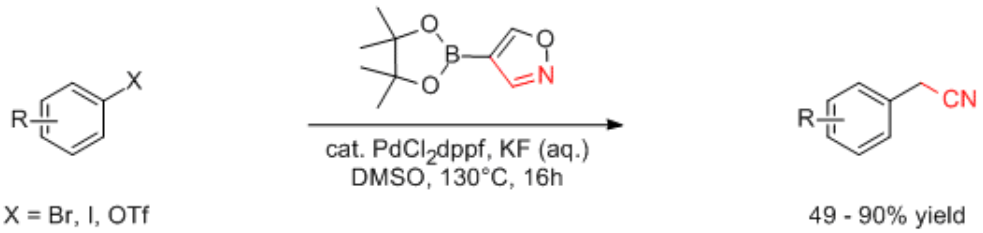
Cyanomethylation of aryl halides by domino Suzuki/fragmentation reaction

J. Velcicky[1], A. Soicke[1,2], R. Steiner[1], H. G. Schmalz[2]*

[1]Novartis Pharma AG, [2]University of Cologne

Arylacetonitrile represents a structural motif found in several drugs including e.g. the anticancer drug Anastrozole. Thanks to the presence of the cyano and the acidic benzylic group it is also a versatile building block for synthesis of more complex organic molecules. Since the classic methods for preparation of arylacetonitriles are often limiting due to their poor functional group tolerance, a Pd-catalyzed alpha-arylation of acetonitrile was explored by several groups during the last decade. While the initial protocols required strong bases and led usually to the bisarylation products [1], these issues could later be overcome e.g. by using trimethylsilylacetonitrile as a reagent [2] or by decarboxylative coupling using cyanoacetate salts [3].



Recently, we could also contribute to this field by developing an efficient method based on the commercially available 4-isoxazole boronic ester [4]. While the reaction was discovered by a chance, we could developed it into a reliable protocol and also prove the interesting cascade reaction mechanism including Suzuki coupling followed by base-induced isoxazole fragmentation and *retro*-Claisen reaction. Under the optimized conditions (*cat*. $PdCl_2$dppf, aq. KF, DMSO, 130°C, 16h), a variety of substrates could be transformed into the corresponding products in good yields. We believe that our method offers an interesting extension to the repertoire of procedures for synthesis of arylacetonitriles. The details on the optimization of reaction conditions as well as the mechanistic studies will be discussed during the presentation.

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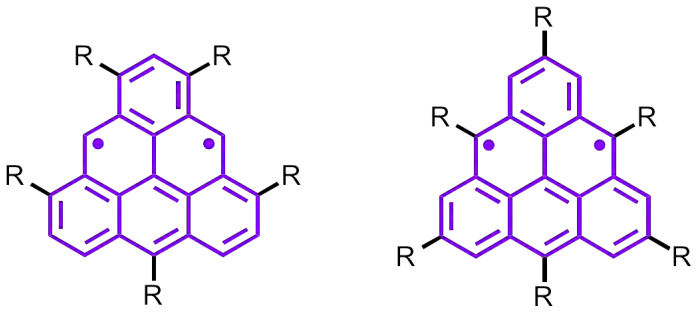
Stabilization of Non-Kekulé Triangulene

M. Juricek[1], T. Solomek[1], P. Ribar[1], P. Ravat[1]

[1]University of Basel

Non-Kekulé graphene fragments (GFs) are promising candidates for applications in future molecular quantum electronic devices. These hydrocarbon molecules have an open-shell electronic structure, which dictates their unique properties but also their high chemical reactivity. Only a handful of open-shell GFs are known to this day. These rather rare examples, however, were only detected under strict oxygen-free conditions and at low temperatures. Our aim is to stabilize a non-Kekulé compound triangulene (in purple, see figure) that contains two unpaired electrons and has a triplet ground state[1]. The first attempt to synthesize this hydrocarbon was carried out by Clar[2] and, to this day, only a single triangulene derivative, detected in solution[1], is known. Our aim is to isolate triangulene as a solid material by embedding its sensitive diradical core inside a protective shell, (i) in the form of a supramolecular complex or (ii) with the aid of bulky peripheral substituents. We have developed a new synthetic approach, which allows us to introduce one to six substituents around the triangulene's core in a highly regioselective manner. Synthesis and characterization of the target compounds will be presented and supported by EPR measurements and quantum chemical calculations.



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Multi-Catalyst Screening for the Asymmetric Morita-Baylis-Hillman Reaction by Mass Spectrometric Monitoring of the Back Reaction

P. Isenegger[1], A. Pfaltz[1]*

[1]Department of Chemistry, University of Basel

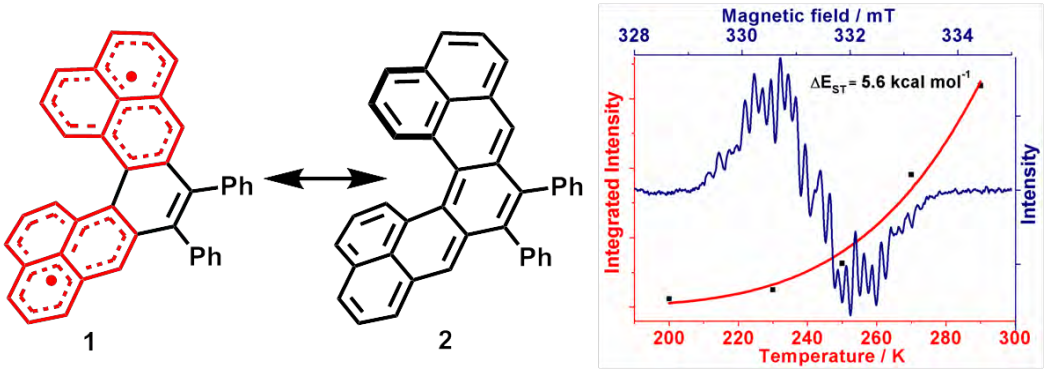
The Morita-Baylis-Hillman (MBH) reaction is a powerful method for the formation of a carbon-carbon bond between the α position of an activated alkene and an electrophile. Although substantial progress has been made in the development of enantioselective MBH reactions, the search for more efficient chiral catalysts with broader scope continues.[1] In our group we have recently developed a new screening method for chiral catalysts, based on mass-labeled quasienantiomeric substrates and electrospray mass spectrometry (ESI-MS).[2,3] This method allows determination of the intrinsic enantioselectivity of a catalyst by mass spectrometric monitoring of catalytic intermediates. ESI-MS-based screening is fast, reliable, and operationally simple as it does not require work-up or purification steps. The screening method was successfully applied to the single catalyst screening with different aminophosphines containing either thiourea- or squaramide-group as additional functional group. Furthermore the potential of the screening protocol for combinatorial catalyst development is demonstrated. A crude catalyst-mixture containing six different organocatalysts was synthesized by a two-step synthetic process and directly used for the simultaneously determination of the selectivity of each single catalyst. In conclusion, we have developed a fast and powerful combinatorial approach for the search of selective organocatalysts for the MBH reaction.

Helically Chiral Biradicaloid Polycyclic Aromatic Hydrocarbon

P. Ravat[1], M. Juricek[1]

[1]University of Basel

The combination of chirality and magnetic properties integrated in a single molecule is scarce, but it could be potentially useful for development of spintronic devices. Helicenes, *ortho* -annelated polycyclic aromatics, benefit from having a non-planar helically chiral π-conjugated structure. By creating a helicene system bearing one or more unpaired electrons, one should thus be able to combine (i) the magnetic property, related to the non-zero spin of a molecule, and (ii) the chiroptical functionality, stemming from the inherent chirality of the same molecule.



We have synthesized the first chiral neutral biradicaloid polycyclic aromatic hydrocarbon **1**. The molecule **1**, is composed of two phenalenyl moieties (red-lined rings), each providing the target structure with one unpaired electron. The phenalenyl moieties are fused to a central benzene ring such that a non-planar [5]helicene backbone is obtained. The electronic structure of this hydrocarbon can be illustrated by several representative resonance forms, for example **1** and **2**. The molecule **1** has a open-shell singlet ground state. At room temperature molecule **1** gave well resolved EPR spectrum for the biradical species. The EPR signal intensity decreases upon decreasing the temperature and almost diminishes at 200 K. The Bleaney Bower's fit gave the large singlet–triplet energy gap of 5.6 kcal mol^{-1}.
The detailed synthetic strategy, structure–property relationship and the theoretical investigation of molecule **1** and its derivatives will be presented during the presentation.

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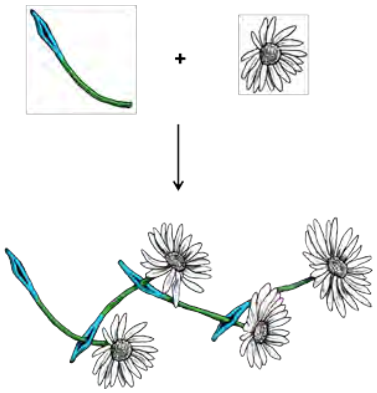
Concentration Controlled Synthesis of Molecular Daisy Chains − Towards [c2]Daisy Chains as Functional Materials

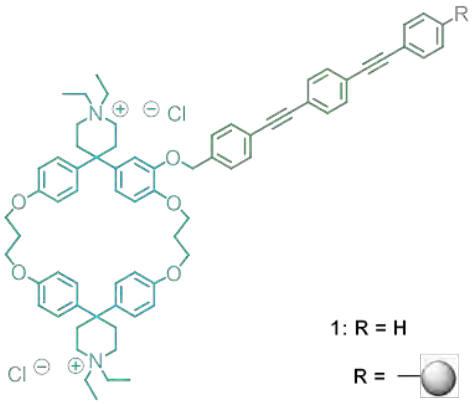
S. Drayss-Orth, Y. Aeschi[1], J. Rotzler[1], M. Mayor[1]*

[1]University of Basel

Inspired by the beautiful pseudo-rotaxane concept of Sauvage[1], we designed organic molecular structures ideally suited for the formation of molecular daisy chains.[2] By functionalizing the periphery of a water-soluble *Diederich*-type cyclophane[3] with a rigid hydrophobic oligo-phenylene ethynylene (OPE) rod, we obtained the amphiphilic monomer **1** which could be fully characterized. Driven by a strong hydrophobic effect, the hermaphroditic molecule forms dimers in polar solvents at very low concentrations (i.e. 10^{-7} mM).[4] This aggregation behavior was investigated in detail and confirmed by ^{1}H-Nmr titrations, DOSY experiments and fluorescence studies.

Encouraged by these initial results, we functionalized the terminal OPE moiety making the aggregates accessible to be captured by a bulky stopper unit. Furthermore, derivatisation at the OPE periphery allows the integration of the mechanically interlinked dimers into functional materials. By attaching a terminal thiol group at the rod, the dimers can potentially be addressed by gold electrodes of a mechanically controlled break junction. Conductance through the resulting bimolecular junction is expected due to a strong intermolecular π-π stacking between the two OPE rods.[5] Mechanical adjustment of the π-overlapping surface results in the variation of conductance. Hence, the thiol functionalized [c2]daisy chain can act as a nanoscale potentiometer.





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Modular Synthesis, Functionalization and resolution of Cationic [6]HELICENES

G. Labrador[1], J. Bosson[1], E. Francotte[2], Z. Breitbach[3], D. W. Armstrong[3], J. Lacour[1]*

[1]University of Geneva, [2]Novartis Institutes for Biomedical Research, [3]University of Texas at Arlington

Helicenes are *ortho*-condensed polyaromatic compounds that are used in a variety of applications.[1] Recently, we have developed a new class of cationic dioxa**1**, azaoxa **2** and diaza **3** [6]helicenes. These derivatives are accessible from a single common precursor at high temperatures (≥170 °C).[2] Herein, in a new development we show that it is possible to transform **1** into **2** and **2** into **3** at only 60 – 70 °C taking the helical strain as advantage. Moreover, compounds **1**, **2** and **3** can be resolved as single enantiomers and transformation from **2** to **3** is then enantiospecific (*es* ≥ 94 %).

Furthermore, dioxa **1** can be post-functionalized by addition of indoles through vicarious nucleophilic substitution reactions.[3] The importance of the different modifications can be evidenced in their strong influence on the optical and chiroptical properties of the luminophores.

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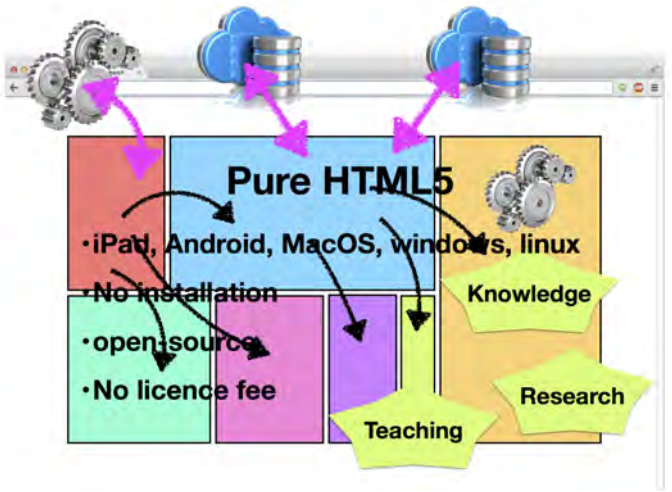
Online swiss army knife for organic chemists

L. Patiny[1], M. G. Zasso[1], D. Kostro[1]

[1]Institute of Chemical Sciences and Engineering ISIC, EPF Lausanne

Most of the experimental results today are saved in databases. However the final goal is not only to store data but also to be able to process and ultimately extract knowledge from it. In this context we have created an open source environment that allows to quickly and easily develop web applications that solve real research problems: the Visualizer[1].

How far can we go ? This presentation will address this question and present the results that were obtained during the last 3 years.



Real case applications will be shown and the underlying innovative algorithm will be explained:

- NMR prediction (1H, 13C, COSY, HSQC, HMBC) and simulation
- NMR peak picking and automatic assignment[2]
- Complex mass spectra analysis based on the monoisotopic mass and isotopic distribution[3]
- Mass spectra analysis of non-natural peptide sequences
- Generation of virtual chemical library with logP, logS and filtering using parallel coordinates
- Wikipedia chemical structure explorer[4]

All those web applications are available publicly for free on the website http://www.cheminfo.org.

[1] https://github.com/npellet/visualizer
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Structure Refinement of a ß-Heptapeptide Using RDCs Measured in a Stretched PVA Gel in Methanol

C. Rigling[1], M.-O. Ebert[1]*

[1]ETH Zurich, Laboratory of Organic Chemistry, Zurich, Switzerland

The use of residual dipolar couplings (RDCs) for the structure calculation of large biomolecules is an established method. For small and medium-sized molecules, however, both experimental determination of RDCs and implementation in structure calculation remain challenging.[1] Especially for (flexible) medium-sized molecules the additional long-range restraints are crucial for better definition of the experimentally derived ensemble.

Here we present the solution structure of a ß-heptapeptide in methanol obtained by NMR structure calculation including RDCs measured in a stretched polyvinyl acetate (PVA) gel in methanol.
In agreement with an earlier qualitative study,[2]the result of a first round of simulated annealing solely based on NOE and dihedral angle restraints shows a well defined 314-helix. In addition a bundle of structures was calculated using also RDCs restraints.
Comparison of the two resulting structural bundles without and with incorporation of RDCs showed an improved long-range precision for the latter. The applied method and the structure calculation process are discussed.

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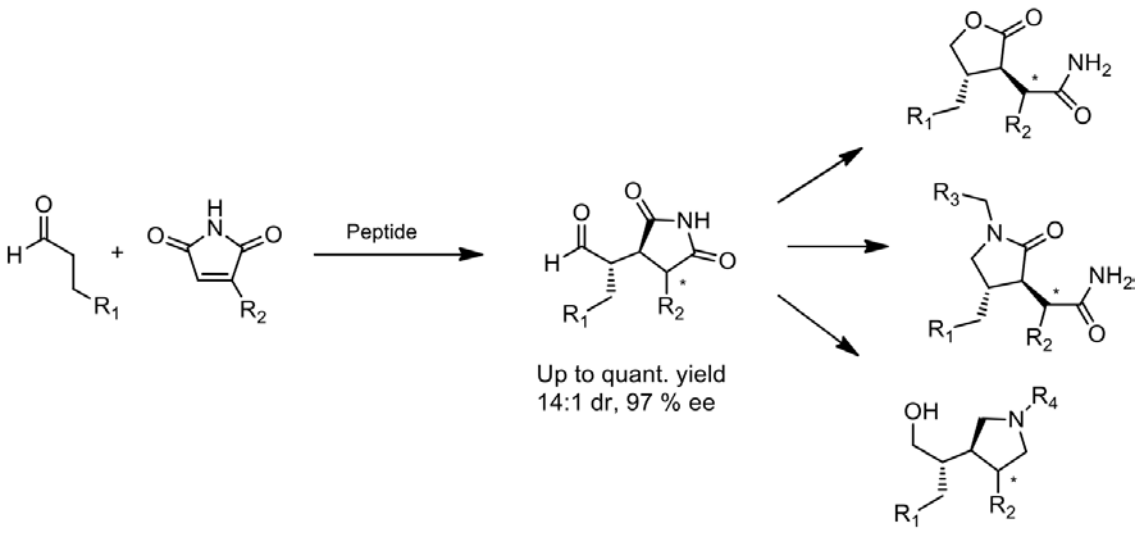
Peptide-Catalyzed Stereoselective Conjugate Addition Reactions of Aldehydes to Maleimides

C. Grünenfelder[1], H. Wennemers[1]*

[1]ETH Zurich, Laboratory of Organic Chemistry, Zurich, Switzerland

Stereoselective conjugate addition reactions of aldehydes to maleimides offer an efficient entry into chiral succinimide derivatives which are present in natural products and drug candidates.[1] Tripeptides of the type Pro-Pro-Xaa (Xaa = acidic amino acid) have been introduced in our group as catalysts for aldol reactions and conjugate addition reactions of aldehydes to *β*-mono, *α,β*- and *β,β*-disubstituted nitroolefins.[2] Herein, we present a highly active and selective peptidic catalyst able to activate aldehydes and maleimides and to control the stereoselectivity of conjugate addition reactions.



Subsequent transformation of the products into lactones, lactams, and pyrrolidines and initial mechanistic data explaining the observed stereoselectivity and activation of the electrophile by the catalyst will also be presented.[3]

[1] P. Chauhan, J. Kaur, S. S. Chimni, *Chem. Asian J.* **2012**, *8*, 328.
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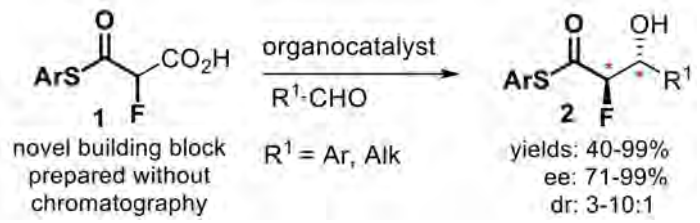
f) R. Kastl, H. Wennemers, *Angew. Chem. Int. Ed.* **2013**, *52*, 7228.

Enantioselective Aldol Reactions with Fluoromalonyl Halfthioesters as Masked Fluoroacetates

J. Saadi[1], H. Wennemers[1]*

[1]ETH Zurich, Laboratory of Organic Chemistry, Zurich, Switzerland

One very long standing challenge in organic chemistry is the enantioselective incorporation of fluoroacetate into organic molecules. Acetate itself is one of the most fundamental building blocks in nature and organic synthesis, and aldol reactions of acetate derivatives are reliable tool to access polyketide architectures. Catalytic asymmetric aldol reaction of fluoroacetate would therefore enable the controlled incorporation of fluorine at defined positions within the medicinally important compounds, thus enhancing their activity and improving their properties.



We have developed an efficient synthesis of fluoromalonic acid halfthioesters **1** (FMAHTs), and applied them as masked fluoroacetates in an aldol reaction. Broad range of aldehydes reacted with FMAHTs under mild organocatalytic conditions, making long sought-after, fluoroacetate aldol products **2** accessible in an enantioenriched form. To demonstrate the practical utility of our methodology we also prepared a fluorinated-derivative of one of the top-selling drugs.

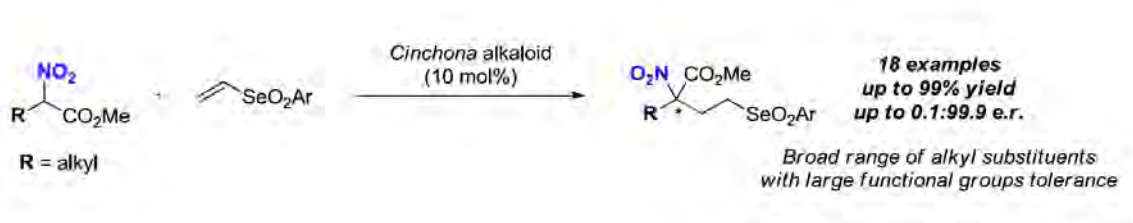
J. Saadi, H. Wennemers, *manuscript submitted*.

Organocatalytic enantioselective Michael addition of α-alkyl substituted α-nitroacetates to phenyl vinyl selenone

A. Clemenceau[1], Q. Wang[1], J. Zhu[1]*

[1]Laboratory of Synthesis and Natural Products, Institute of Chemical Sciences and Engineering, Ecole Polytechnique Fédérale de Lausanne, EPFL-SB-ISIC-LSPN, BCH5304, CH-1015 Lausanne, Switzerland

Synthesis of enantio-enriched α-quaternary α-amino-acids has remained an active research area. We have recently described a *Cinchona* alkaloid-catalyzed Michael addition reaction of methyl α-aryl-α-isocyanoacetates to phenyl vinyl selenone. The resulting enantioenriched α-aryl-α-(2'-phenylselenonylethyl)- α-isocyanoacetates were subsequently converted into α-aryl-α-(2'-FG-alkyl)- α-amino acids and medicinally important heterocycles as well as natural product trigonoimine A.[1] To access α,α-dialkyl substituted α-amino acids, a novel *Cinchona* alkaloid-catalyzed enantioselective Michael addition reaction has been developed using α-alkyl substituted α-nitroacetates and phenyl vinyl selenone as reaction partners. Under optimized conditions, α-alkyl-α-(2'-phenylselenonylethyl)-α-nitroacetates were obtained in good to excellent yields and enantioselectivities. The broad substrate scope and the easy modification of the nitro and phenylselenonyl groups made this reaction a useful alternative for the synthesis of α,α-dialkyl substituted α-amino acids and other chiral building blocks.[2]



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CHIMIA

CHIMIA 2015, Volume 69
ISSN 0009-4293
www. chimia.ch

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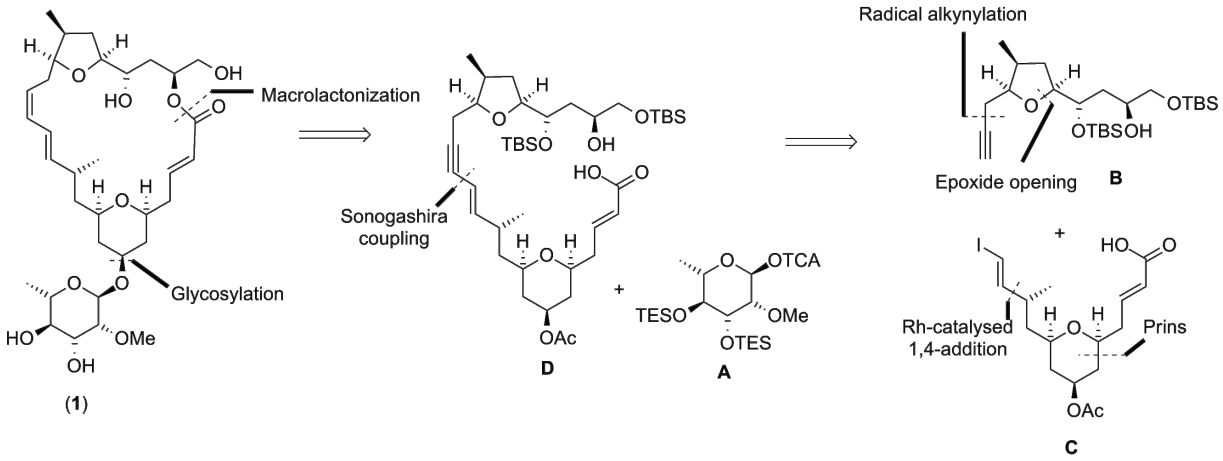
Total Synthesis of Mandelalide A

T. Brütsch[1], K.-H. Altmann[1]*

[1]ETH Zürich

Mandelalide A (**1**) is a glycosylated marine macrolide that was isolated in 2012 from a new *Lissoclinum* species and was found to exhibit significant cytotoxicity to human NCI-H460 lung cancer and to mouse Neuro-2A neuroblastoma cell lines. [1]



In the context of our general interest in biologically active natural products with potential anticancer activity, we embarked on the total synthesis of **1**, in order to provide material for additional biological testing and to establish a chemical basis for eventual SAR studies.

As depicted above, our synthesis of mandelalide A (**1**) [2] is based on building blocks **A**, **B** and **C** as advanced intermediates. Key steps are a macrolactonization of **D** followed by a *Z*-selective reduction of the alkyne moiety and a late stage glycosylation with glycoside donor **A**. Seco acid **D** was assembled by Sonogashira cross-coupling of fragments **B** and **C**. The synthesis **B** includes a rarely used radical alkynylation reaction and an epoxide opening strategy to form the tetrahydrofuran ring. The tetrahydropyran fragment **C** was obtained via a rhodium-catalyzed enantioselective 1,4-addition of TMS-acetylene to crotyl aldehyde and a Prins cyclization to obtain the tetrahydropyran moiety.

This contribution will discuss the details of the total synthesis of mandelalide A (**1)** and provide insight into its unexpected bioactivity profile.

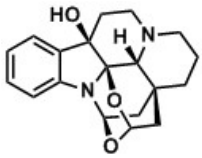
[1] McPhail et al., *J. Org. Chem*. **2012**, *77*, 6066.
[2] For the first total synthesis of **1** see: Xu *et al*., *Angew. Chem. Int. Ed.* **2014**, *53*, 6533.

First Enantioselective Total Synthesis of Terengganensine A

C. Piemontesi[1], R. De Matos[1], Q. Wang[1], J. Zhu[1]*

[1]EPF Lausanne

Terengganensine A, an eburnane indole alkaloid, was isolated in 1997 from *Kopsia terengganensis* by Païs and coworkers.[1] This heptacyclic compound contains an unusual cage-like structure involving the indole nitrogen with six stereogenic centers, one acetal and two aminal functions.



7 steps from commercially available materials
16% overall yield and 95:5 e.r.
Full control of the diastereoselectivity
Confirmation of the absolute configuration

We report herein the first enantioselective total synthesis of terengganensine A.[2] Starting from simple commercially available starting materials, we obtained terengganensine A in 7 steps and 16% overall yield with complete diastereocontrol and 95:5 enantiomeric ratio.

This synthesis also confirmed the absolute configuration of the natural product.

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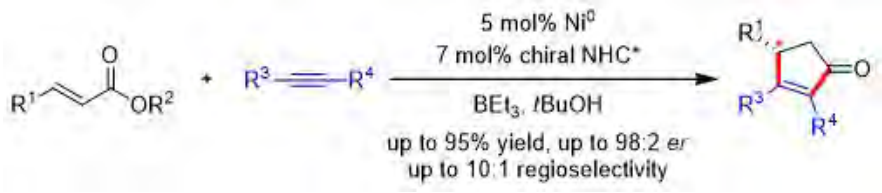
Synthesis of Cyclopentenones by an Asymmetric Nickel-Catalyzed [3+2] Reductive Cycloaddition of Enoates with Alkynes

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

[1]EPF Lausanne

Amongst the members of the family of five membered carbocyclic rings, cyclopentenones are of utmost importance in chemistry. They are found in numerous natural and synthetic products and also are versatile building blocks in several routes towards the synthesis of complex molecules.[1] Thus, the generation of cyclopentenones in a straightforward manner from readily available substrates remains an important target.

Several transition metal-catalyzed reactions for accessing cyclopentenones have been reported over the past years,[1] including an intermolecular nickel-catalyzed [3+2]-cycloaddition of enoates with alkynes.[2,3] We report an asymmetric nickel-catalyzed [3+2] reductive cycloaddition of enoates with alkynes using a chiral bulky C_1-symmetric N-heterocyclic carbene ligand to provide an efficient highly yielding and enantioselective route to chiral cyclopentenones from simple, stable, and readily available acyclic π-systems.[4]



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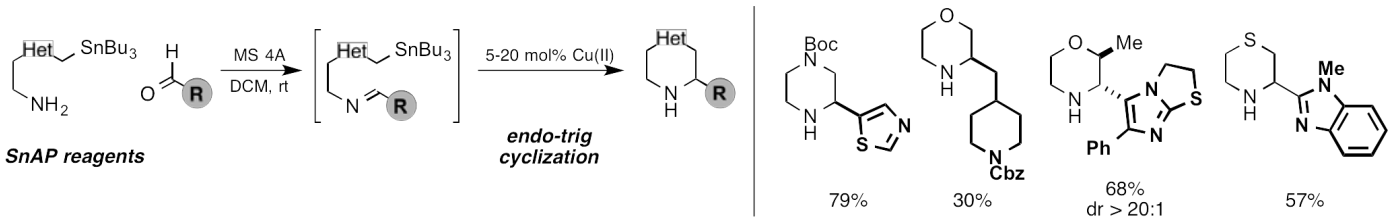
Catalytic One-Step Synthesis of Unprotected Piperazines, Morpholines and Thiomorpholines using SnAP Reagents

M. U. Luescher[1], J. W. Bode[1]*

[1]ETH Zurich

Saturated N-heterocycles have long been considered as privileged elements for the preparation of bioactive small molecules. Increasing recognition of problems associated with heteroaromatic pharmacophores, such as poor solubility, bioavailability, or pharmacokinetics have further enhanced their importance in drug development. [1] Despite this, their synthesis often requires long, laborious synthetic routes to form these ring systems, including the need for protecting groups. To directly access a variety of fully saturated N-heterocycles in a single synthetic operation, we have recently introduced SnAP (Stannyl Amine Protocol) reagents, which convert aldehydes and ketones directly into morpholines, piperazines, diazepanes, thiomorpholines, spiro- and other N-heterocycles. [2–6]



The major limitation using the SnAP reagents is the need for stoichiometric copper reagents. We have now identified new ligands and conditions that render the reaction catalytic in copper and expanded the substrate scope to α-bis(substituted) SnAP reagents. These studies, including approaches towards an enantioselective process and insights into the unique reaction mechanism, will be discussed.

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Organocatalytic Atroposelective Aldol Condensation

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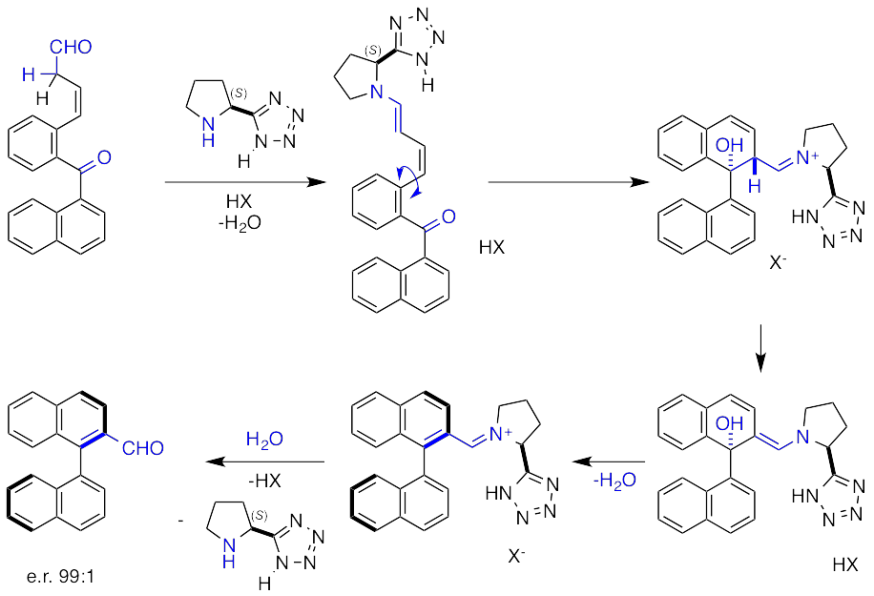
[1]University of Basel

Axially chiral compounds are important building blocks for various applications, e.g. in ligand design. Despite the importance of atropisomers such as binaphthyl derivatives, only few stereoselective methods are available for their synthesis.

A catalytic method was developed that converts ketoaldehyde precursors into tri-*ortho*-substituted biaryls upon treatment with a pyrrolidinyl-tetrazole catalyst. The stereochemical information is thereby efficiently transferred from the catalyst into the axial chirality of the product. Initially, an activated dienamine is formed to trigger a subsequent cyclization followed by a second α-deprotonation. This activates for a dehydration step leading to the formation of an aromatic ring providing sufficient driving force for the reaction. Hydrolysis to regenerate the catalyst gives the binaphthalene-carbaldehyde with an e.r. = 99 :1.



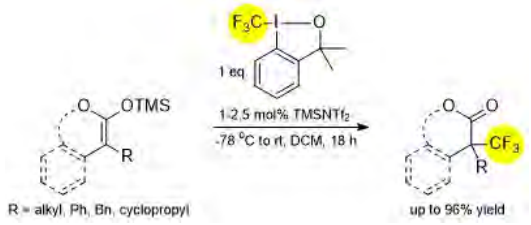
A. Link, C. Sparr, *Angew. Chem.* **2014**, *126*, 5562–5565; *Angew. Chem. Int. Ed.* **2014**, *53*, 5458–5461.

Lewis Acid Catalyzed Electrophilic Trifluoromethylation of Silyl Ketene Acetals: Access to Quaternary α-Trifluoromethylated Esters and Lactones

D. Katayev[1], V. Matoušek[1], R. Koller[1], A. Togni[1]*

[1]ETH Zurich

Herein we describe an efficient Lewis acid-catalyzed trifluoromethylation of silyl ketene acetals using a hypervalent iodine-CF_3-reagent as an electrophilic source of CF_3.[1-2] The mild reaction protocol provides direct access to quaternary α-trifluoromethylated esters and lactones in up to 96% isolated yield using only 1-2.5% of trimethylsilyl triflimide ($TMSNTf_2$) as catalyst. It is noteworthy that the reaction of cyclic ketene acetals is rather insensitive to steric bulk, with excellent yields for isopropyl, tert-butyl and cyclohexyl-substituted lactones. The 5-, 6- and 7-membered α-trifluoromethylated lactones were successfully prepared by this method. Cyclic α-aryl-substituted silyl ketene acetals reacted sluggishly, whereas α-heteroatom-substituted substrates gave complex reaction mixtures. Mechanistic studies led to conclude that free radical intermediates are unlikely in this transformation, although they cannot be ruled out with certainty.



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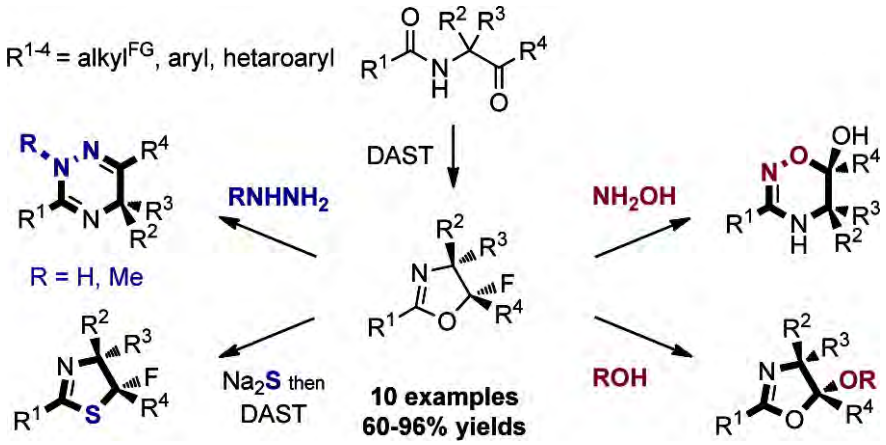
DAST-mediated Cyclization of a,a-Disubstituted-a-acylaminoketones: Efficient and Divergent Synthesis of Unprecedented Heterocycles

A. Bigot[1], O. Loiseleur[1]

[1]Syngenta Crop Protection AG

The ligand-based rational design of a new insecticidal ecdysone agonist will be presented.[1] Synthetic efforts towards this unprecedented fluorooxazoline scaffold further led to the discovery of a DAST-mediated cyclization of α,α-disubstituted -α-acylaminoketones. Mechanistic studies revealed that the resulting products can be ring-opened or selectively substituted by a range of nucleophiles to provide in high yields a diverse array of novel heterocyclic frameworks.[2]



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Design, synthesis and properties of 'Photochomic Torsional Switches' (PTS)

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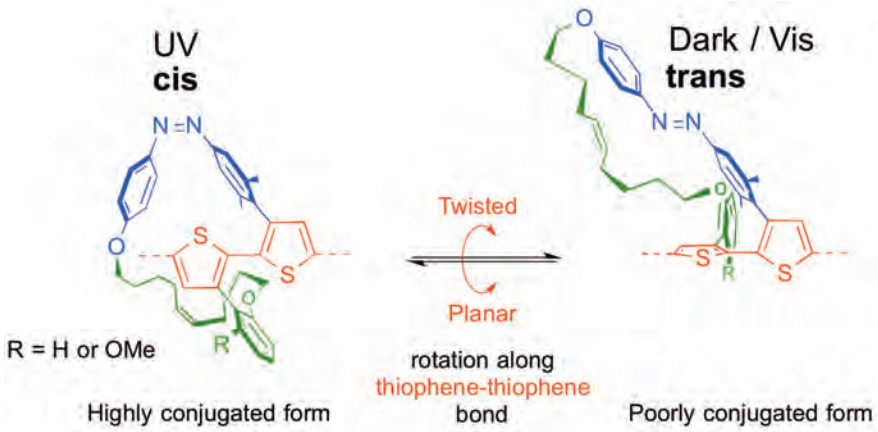
[1]École Polytechnique Fédérale de Lausanne (EPFL)

The geometrical arrangement of the p-orbitals in organic semiconductors plays a pivotal role for the optoelectronic properties of the resulting bulk materials.[1] Control over the π-bond geometry, e.g. the planarity, of an extended conjugated system offers the possibility to modulate the effective conjugation length of a π-system, thus, allowing for the tuning of optical and electronic properties.[1,2] A promising way to reversibly modulate the orientation of the p-orbitals in a conjugated strucrure is to incorporate photochromic segments onto the 'backbone' of the π-system. Attempts to use photochromic molecules as monomer units in a polymer chain have shown that the photo-reversibility efficiency decreases inversely with the enhancement of the π-conjugation.[3] In the present work we report on a novel molecular architecture, referred to as a 'photochromic torsional switch' (PTS), which can overcome the limits of todays photochromic dyes towards their incorporation into extended π-system. The aforementioned molecular structure consists of a polymerizable bithiophene unit able to mechanically change its π-system planarity in response to a photochromic isomerization of a laterally attached azobenzene unit. In the dark and upon exposure of visible light, the azobenzene moiety assumes its extended *trans* conformation, thus, forcing the bithiophene backbone to twist out of coplanarity (dihedral angle from 50° to 68°). By contrast, exposure to UV light results in isomerization of the azobenzene unit to the *cis* conformation, which allows the bithiophene fragment to assume a planar, π-conjugated conformation (dihedral angles from 150° to 168°). The PTS architectures, proposed in this work, represent a new generation of photochromic dyes that can allow for the preparation of 'conjugated photochromic polymers', and help to gain deeper understanding of the correlation between molecular conformation and optoelectronic properties of π-conjugated macromolecules.



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[2] R. Rieger, D. Beckmann, A. Mavrinskiy et al.,*Chem. Mater.*,**2010**, 22, 5314-5218
[3] F. Stellacci, C. Bertarelli, F. Toscano et al.,*Adv. Mater.*,**1999**, 11, 292-295

Dancing Ladders - Inducing and Distorting Helical Chirality in Achiral Polycyclic Systems

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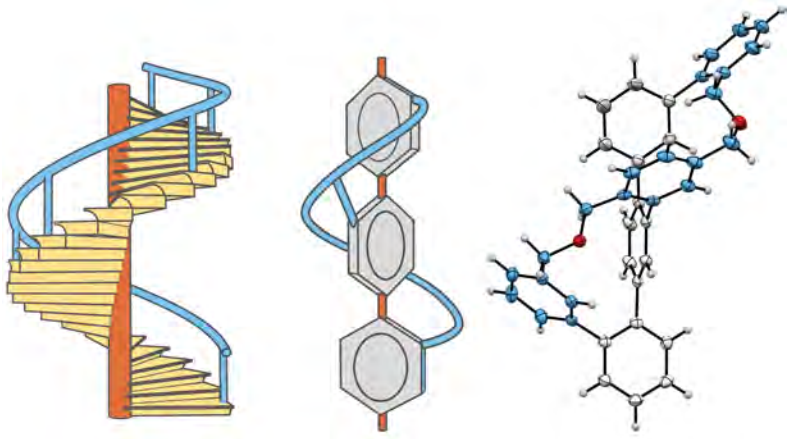
[1]University of Basel

Recently we presented an exciting new concept in ***Angewandte Chemie***[1a,b] how to introduce helicity to a polyaromatic system by interlinking two oligomer strands of different lengths. To compensate for the dimensional mismatch, the longer oligomer wraps around the oligophenyl backbone. The obtained "Geländer"- (or bannister-) oligomers resemble helical staircases or pirouetting dance ribbons.



The new helical polyaromatics were fully characterized including X-ray diffraction analysis. Because the obtained helical structures lack a point of inversion they exist exclusively as one set of enantiomers. The isolation of the pure enantiomers enabled the chiroptical properties as well as the racemization process to be studied by circular dichroism spectroscopy. The targeted variation of the interlinking heteroatom allowed varying the degree of twist and studying the resulting heights on the racemization barriers.[2] By mismatching the oligomeric strands it was possible to distort the induced helicity and investigate the impact on the dynamics of the system.[2]

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[2] Manuscripts in preparation

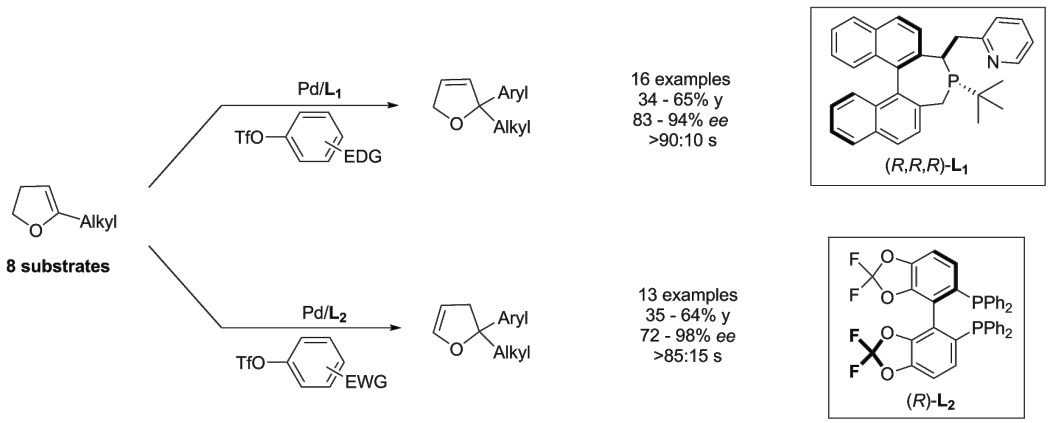
Access to dihydrofurans with a fully substituted C2 stereocenter by Pd-catalyzed intermolecular asymmetric Heck reaction

G. M. Borrajo-Calleja[1], V. Bizet[1], T. Bürgi[1], C. Mazet[1]*

[1]University of Geneva

During the past decades, the asymmetric *intramolecular* Heck reaction has been successfully applied in natural product synthesis to install tertiary and quaternary stereocenters.[1] Surprisingly, the *intermolecular* asymmetric version of the reaction has not reached the same level of development. To date, it has been used essentially as a benchmark reaction to validate the design of novel homotopic and heterotopic chiral bidentate ligands. Systematic studies with emphasis on expanding the scope of substrates are scarce.[2,3]

Herein we describe a highly selective methodology that gives access to chiral 2,3 and 2,5 dihydrofurans with a fully substituted C2 stereocenters. Under identical experimental conditions, with our homemade (P,N) ligand **L1** or the commercially available (P,P) ligand **L2**, 2,5 or 2,3-dihydrofurans can be obtained respectively with high enantioselectivity, regioselectivity and good yields.[4]



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[4] G. M. Borrajo-Calleja, V. Bizet, T. Bürgi, C. Mazet *Submitted*.

Domino Reaction to Functionalize Heterocycles: A Complementary Method to C-H Functionalization

Y. Li[1], J. Waser[1]*

[1]EPF Lausanne

Molecules containing heterocycles and alkynes play an important role in medicinal chemistry and material science.[1] A well-established method – the Sonogashira reaction- has dominated the introduction of alkynes onto heterocycles. Due to several shortcomings of the Sonogashira reaction as stoichiometric waste and poor stability or difficult accessibility of starting materials, a more direct and regioselective fashion is highly desirable.

Based on the previous work in our group,[2] a direct alkynylation method was first developed to access *C2* alkynylated furans and benzofurans with gold catalyst and benziodoxolone reagents.[3] In the case of benzofurans, $Zn(OTf)_2$ was discovered as a new and efficient reagent to activate alkynylated hypervalent iodine reagent.[3b]

Although C-H direct alkynylation provides a straightforward way to access these alkynylated heterocycles, there are still several shortcomings to consider. One of the most serious issues is that the functionalized positions are limited on heterocycles because of its inherent reactivity. It is therefore intriguing and challenging to find an alternative way to functionalize other positions. Domino reactions could provide a solution to this challenge, as the metal-carbon bond could be installed on positions different from the ones obtained by direct metallation pathway.

Starting from 2012, we spent intensive effort on developing a cyclization-alkynylation domino reaction to functionalize *C3* position on furan, with discovering that bistriflroromethyl benziodoxole reagent is an exceptionally efficient reagent for this process with gold (III) catalyst.[3a] Then we turned our interest to more challenging positions, *C5* and *C6* on benzene part of indoles. Platinum (II) catalyst showed superior reactivity towards carbon nucleophile cyclization –alkynylation process.[4]

Combining two approaches, a series of alkynylated hetercycles could be rapidly accessed. Further functionalization of these compounds could construct several unprecedented building blocks for organic material science. Developing new domino process with different metal catalysts and electrophilic reagents could be envisaged as the next step.

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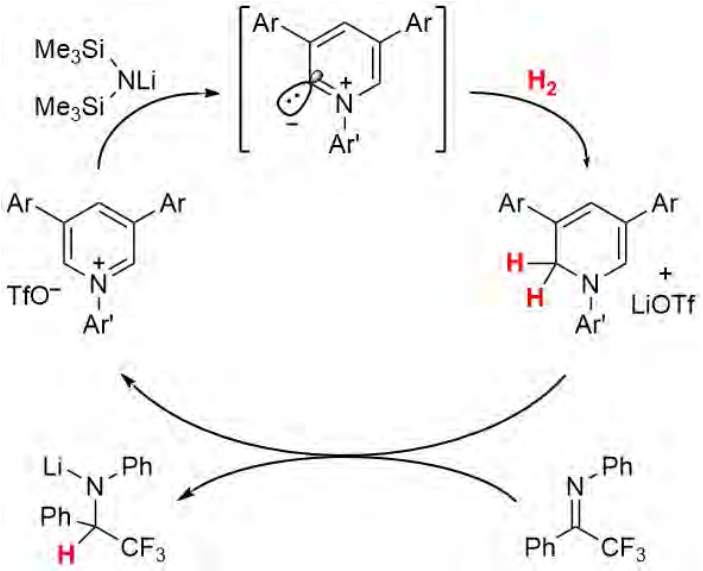
Pyridylidene-Mediated Dihydrogen Activation Coupled with Catalytic Imine Reduction

J. Auth[1], A. Pfaltz[1]*

[1]University of Basel

In recent years dihydrogen activation at non-metallic centers has found increasing attention. A breakthrough in the development of non-metallic catalytic systems for H_2 activation was achieved by Stephan and Erker, based on the concept of Frustrated Lewis Pairs (FLPs).[1] We developed a system in which dihydrogen is trapped by a pyridylidene intermediate that is generated from a pyridinium salt and base. This process has precedent in the H_2 addition to an aminocarbene reported by Bertrand and coworkers. [2] However, in contrast to the amine produced from an aminocarbene, dihydropyridine resulting from H_2 addition to a pyridylidene can act as reducing agent toward organic electrophiles. By coupling the hydrogen activation step with subsequent hydride transfer from the dihydropyridine to an imine, a catalytic process was established.



Scheme 1. Proposed catalytic cycle.

[1] Reviews: a) D. W. Stephan, G. Erker, *Angew. Chem. Int. Ed.* **2010**, *49*, 46; b) G. Erker, *Pure Appl. Chem.* **2012**, *84*, 2203; c) D. W. Stephan, *Org. Biomol. Chem.* **2012**, *10*, 5740; d) J. Paradies, *Angew. Chem. Int. Ed.* **2014**, *53*, 3552; e) L. Hounjet, D. W. Stephan, *Org. Process Res. Dev.* **2014**, *18*, 385.
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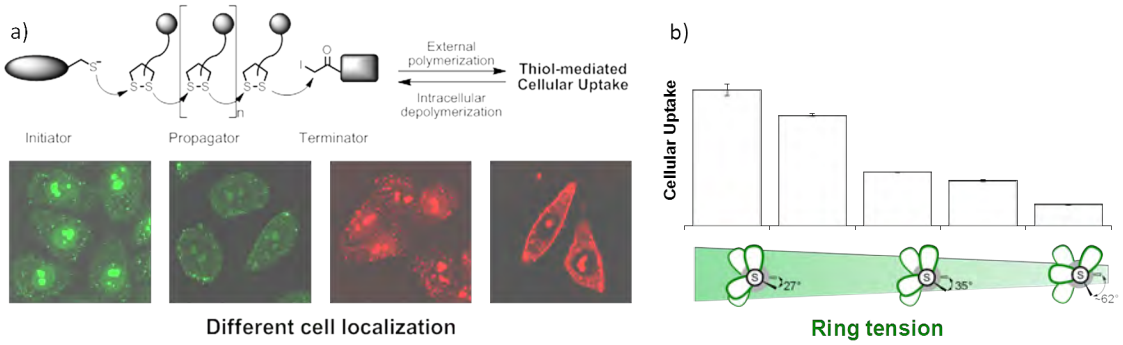
Disclosing a Novel Way for Poly(disulfide)s to Enter Cells

G. Gasparini[1], D. Abegg[1], A. Adibekian[1], N. Sakai[1], S. Matile[1]*

[1]University of Geneva

We recently introduced a new methodology for the synthesis of cell-penetrating poly(disulfide)s, based on substrate-initiated polymerization (siCPDs).[1] Molecules of free choice are used as initiators for ring-opening disulfide-exchange polymerization, linking them covalently to the transporter. After cellular uptake, siCPDs are readily depolymerized by endogenous glutathione, releasing the substrate and providing optimal biocompatibility (Fig. 1a).[2] We also reported the major role played by molecular weight of the siCPDs on cellular localization: it influences the depolymerization kinetics and thus dictates the accumulation of the polymer in endosomes, cytosol or nuclei.[3]



We are now focused on the hypothesis that disulfide bonds not only impact cell localization, but also enhance transmembrane activity. To prove this proposed thiol-mediated uptake mechanism, we prepared a collection of fluorescent probes equipped with different thiols and disulfides. Experiments on living cells clearly indicate that the presence of disulfides, especially under ring tension, enhances the overall uptake (Fig. 1b), suggesting a new energy-dependent pathway that can be exploited to enter into cells.[4] Pull-down proteomics are ongoing in order to identify if and which proteins are involved in the process, towards the delivery of larger substrates.

[1] E.-K. Bang, G. Gasparini, G. Molinard, A. Roux, N. Sakai, S. Matile, *J. Am. Chem. Soc.* **2013**, *135*, 2088-2091.
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[4] G. Gasparini, G. Sargsyan, E.-K. Bang, N. Sakai, S. Matile, *Angew. Chem. Int. Ed.* **2015**, in press.

Halogen Bonding Supramolecular Capsules

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[1]Laboratorium für Organische Chemie, ETH Zürich, Vladimir-Prelog-Weg 3, 8093 Zurich, Switzerland

Molecular capsules based on solely the interaction of halogen bonding (XB) are presented along with their host–guest binding properties.[1] The first example of a well-defined four-point XB supramolecular system is realized by decorating resorcin[4]arene cavitands with polarized halogen atoms for the dimerization with tetra(4-pyridyl) resorcin[4]arene cavitands. NMR binding titrations for F, Cl, Br, and I cavitands as XB donor show association constants K_a up to 5370 L mol^{-1} (ΔG = –4.85 kcal mol^{-1}, for I) even in XB-competitive solvent such as benzene/acetone/MeOH 70:30:1, where comparable monodentate model systems show no association. XB binding is evidenced by 2D HOESY NMR, and the thermodynamic profile shows the largely enthalpic driven nature of the cooperative binding, as predicted earlier by our model system studies.[2]

With these results in hand, we provide detailed experimental data on all halogens (I, Cl, Br, and F) with respect to their XB binding properties. The presented capsular architecture shows the emerging impact of even weak XB interactions for their contribution in future supramolecular chemistry, especially in the context of modern ligand design for medicinal chemistry and crop science.[3]

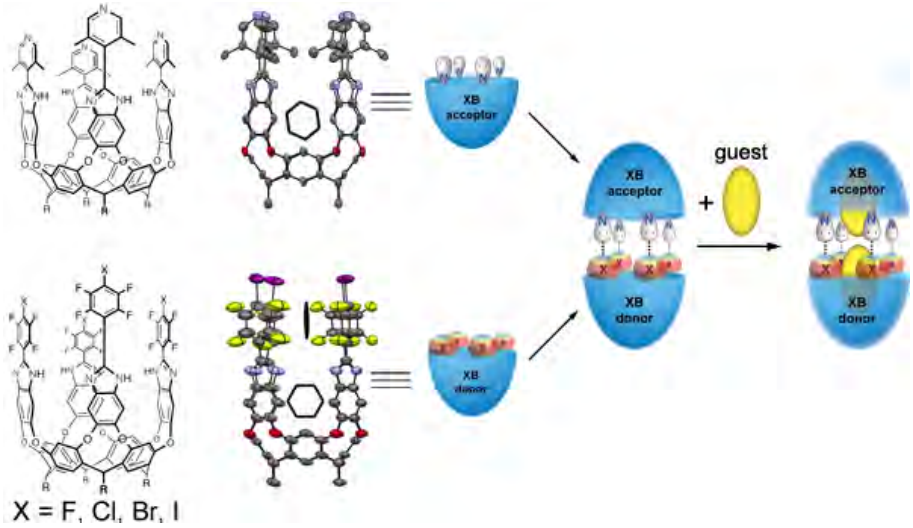

Figure 1. Resorcin[4]arene cavitands as XB acceptor (top) and XB donor hemispheres (bottom) for the assembly of XB molecular capsules. The X-ray structures show each cavitand (X = I) in its *vase* conformation with encapsulated benzene molecules (50% probability ellipsoids, 100 K). Upon mixing of the two components in solution, the formation of XB molecular capsules takes place.[1]

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