1

Mass Spectrometric Screening of Chiral Catalysts

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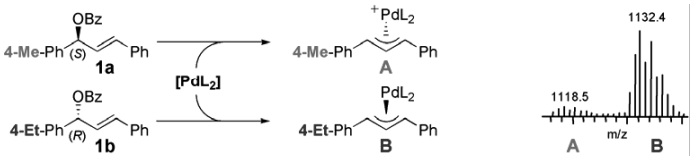
We have developed a new screening method for chiral catalysts, based on mass-labeled, pseudoenantiomeric substrates and electrospray mass spectrometry as an analytical tool. Using this method, the enantioselectivity of chiral palladium catalysts in the kinetic resolution of allylic esters was determined by mass spectrometric monitoring of allyl-Pd intermediates **A** and **B** derived from pseudoenantiomeric substrates **1a** and **1b**. In contrast to conventional screening methods, which are based on product analysis, the intrinsic selectivity of a catalyst can be determined in this way. In addition, simultaneous screening of catalyst mixtures in homogeneous solution is possible.



[1] C. Markert, A. Pfaltz, *Angew. Chem. Int. Ed.* **2004**, *43*, 2497.

2

Tuning the Properties of Emissive Lanthanide Probe Complexes

Filip Kielar, Robert Poole, Robert Pal and David Parker

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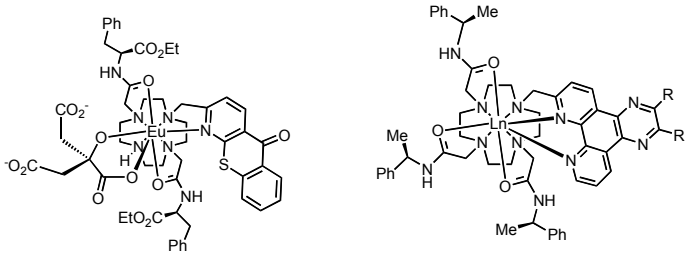
Different strategies have been developed that allow modulation of sensitised lanthanide luminescence to provide information about the local environment of a probe complex. Key issues have been the nature and size of the sensitiser's singlet/triplet energy gap, the facility of inter-system crossing and the degree of control over quenching processes involving the three salient excited states i.e. the singlet and triplet states of the sensitising chromophore and the longer lived lanthanide excited state. Complexes engineered to report on the local concentration of bioactive species such as pH, citrate, and phosphorylated Tyr sites have been devised [1]. In addition, various charged complexes have been studied that show a marked tendency to be taken up by cells. Some of these complexes bind reversibly to DNA and localise selectively in the cell nucleus [2]. Strategies that may serve to allow their practicable usage *in vitro* or *in cellulo* will be aired.



[1] P. Atkinson, Y. Bretonniere, D. Parker, *Helv. Chim. Acta*, **2005**, *88*, 391
[2] R. Poole, G. Bobba, J-C. Frias, M. J. Cann, D. Parker, *OBC*, **2005**, 1013

3

"Measuring" Electron Delocalization in π–Conjugated Compounds

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Even though just a concept, electron delocalization still is a useful und widely used tool to make structure and property predictions for unsaturated compounds (linearly π-conjugated or aromatic). We will present a scheme based on the Natural Bond Orbital analysis of Weinhold allowing to "measure" the delocalization energy along a given path in a π-conjugated system [1,2].

Applications of the scheme of analysis to donor/acceptor functionalized ethynylethenes and cyanoethynylethenes show that contrary to common expectation *cross* (or geminal) *conjugation*, relative to *through conjugation* (cis/trans), is not always a loosing proposition, and that proper functionalization can make a geminal conjugated path more efficient than its through-conjugated counterparts [3,4].

The method presented maps relatively complex information (first-order density matrix generated by the appropriate quantum chemical method) onto quite simple concepts (local contributions to delocalization energy), in the spirit of the word saying that "after every great quantum computation there is a chemical explanation".

[1] M. Bruschi, M.G. Giuffreda, H. P. Lüthi, *Chem. Eur. J.* **2002**, *8*, 4216
[2] M. G. Giuffreda, M. Bruschi, H. P. Lüthi, *Chem. Eur. J.* **2004**, *10,* 5671
[3] M. Bruschi, M.G. Giuffreda, H. P. Lüthi, *Chimia,* **2005**, in press
[4] M. G. Giuffreda, H. P. Lüthi, N. Moonen, F. Diederich, manuscript in preparation

4

Synthesis of Marine Polyketides as Promising Anticancer Agents

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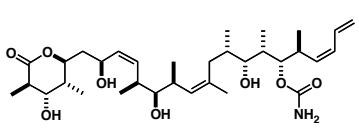
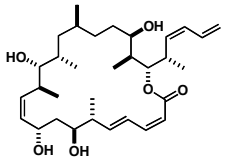
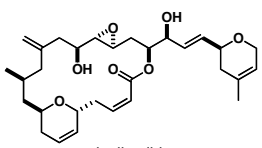
Marine organisms, particularly sponge invertebrates and associated bacteria, are enormously rich sources of structurally diverse secondary metabolites, with important biological activities. In particular, many marine polyketides demonstrate potent cell growth antiproliferative properties and offer promise as lead structures for the development of new anticancer agents, provided the supply issue can be resolved. For the majority of these cytotoxic polyketides, interference with the polymerization dynamics of the major protein components, tubulin and actin, of the cytoskeleton appear to be the two predominant mechanisms of action. Some examples of tubulin-interacting agents include discodermolide, laulimalide, peloruside A and dictyostatin – as shown below. Recent work directed towards the practical synthesis of these polyketides and novel structural analogues will be described.



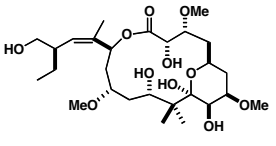
discodermolide



dictyostatin



laulimalide



peloruside A

5

Generation of Homochiral Oligopeptides via "Mirror Symmetry Breaking" in 2-d and 3-d Crystalline Self-Assemblies

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The origin of chirality is one of the yet unsolved problems in pre-biotic chemistry and early evolution. The problem is usually tackled on the basis of two different research directions: the one deals with the origination of an initial enantiomeric excess (e.e), the second focus on the amplification of this e.e. up to a theoretical degree of homochirality. Of particular interest is the pre-biotic formation of homochiral biopolymers, such as primitive polypeptides, and polynucleotides by amplification processes. Current theories suggest that such polymers had been formed at surfaces of minerals or within primitive amphiphilic self-assemblies in the form of vesicles or micelles systems that serve as pre-biotic proto-cells. We shall present a plausible way for attaining homochiral oligopeptides via a "spontaneous mirror symmetry breaking" by a two-step process comprising self-segregation of racemates of activated amino acids into enantiomorphous or racemic domains within 2-d or 3-d crystalline architectures, followed by lattice controlled chemical transformations. We shall describe experiments where racemic mixtures of oligo-peptides of homochiral sequence were produced from racemic mixtures of monomers of activated amino-acids in the form of thio-esters or *N*-carboxy-anhydrides, as 2D crystalline monomolecular films self-assembled at the air/water interface, or within a membrane-like environment in the form of phospho-lipid monolayers or via reactivity within 3-D crystals of *N*-carboxyanhydrides of *D,L* Phenyl-Alanine and *D,L* Valine suspended in aqueous solutions.[1].

[1] H. Zepik *et al Science* **2002**, *295*, 1266; I. Rubinstein *et al Helv. Chim. Acta* **2003**, *83*, 3851; J. G. Nery *et al Angew. Chem. Int. Ed.* **2003**, *42*, 2157; I. Weissbuch, L. Leiserowitz, M. Lahav *Top. Curr. Chem.* **2005**, in press; J.G. Nery *et al Chem.Eur. J.* ***2005***, *11*, 3039.

6

Towards Oligoribonucleotide Foldamers

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RNA features strictly sequence-dependent secondary elements, transmits information, interacts with compounds of different size, and is catalytically active, justifying a search for RNA mimics. Many nucleic acid analogues are known. All differentiate structurally between a contiguous backbone and pending nucleobases. Is this differentiation functionally necessary, or will RNA analogues that integrate the nucleobases into the backbone form duplexes and sequence dependent secondary structures?
We prepared several oligonucleotide analogues with a nucleobase-integrating backbone, restricting ourselves to partially protected adenosine (A) and uridine (U) derivatives. The analogues studied in most depth possess a thiomethylene linker attached to C(5') and either C(8) or C(6) of A or U, respectively. The corresponding dimers associate in chloroform solution with ΔH and ΔS values that depend strongly upon the protecting groups of $C(8)CH_2OH$ and $C(5')CH_2OH$. These dimers pair *via* reverse *Hoogsteen* hydrogen bonding, while a tetramer, associating more strongly and adopting one major conformation, pairs by forming an incipient helix that shows base stacking and *Watson-Crick* (or reverse *Watson-Crick*) hydrogen bonding. Synthesis, pairing properties, and structural models of these and related compounds will be presented.

[1] A. J. Matthews, P. K. Bhardwaj, A. Vasella, *Chem. Commun.* **2003**, 950.
[2] S. Eppacher, N. Solladié, A. Vasella, *Helv. Chim. Acta* **2004**, *87*, 2926.
[3] S. Eppacher, P. Kumar Bhardwaj, B. Bernet, J. L. Bravo Galán, T. Knöpfel, A. Vasella, *Helv. Chim. Acta* **2004**, *87*, 2969.
[4] S. Eppacher, M. Christen, A. Vasella, *Helv. Chim. Acta* **2004**, *87*, 3004.

7

Biphasic Organometallic Catalysis with Water-Soluble Ruthenium(II) Complexes

Ágnes Kathó,[1] Marianna Fekete,[1] Gábor Papp,[2] Gábor Laurenczy,[3] and Ferenc Joó[1,2]

[1]Institute of Physical Chemistry, University of Debrecen and [2]Research Group of Homogeneous Catalysis, Hungarian Academy of Sciences, Egyetem tér 1, H-4010 Debrecen, Hungary; [3] EPFL, Institut des Sciences et Ingénierie Chimiques, LCOM BCH, CH-1015 Lausanne, Switzerland

Of the several aims of green chemistry, the use of environment-friendly solvents and atom economic, preferably catalytic processes are efficiently realized by aqueous-phase organometallic catalysis.

The selectivity of the hydrogenation of unsaturated aldehydes catalyzed by $[\{RuCl_2(m\text{tppms})_2\}_2]$ (*m*tppms = monosulfonated triphenylphosphine) strongly depends on the pH of the aqueous phase [1] and on the H_2 pressure [2]. In order to identify the catalytically important Ru(II) hydrides, detailed ^{1}H-NMR studies were performed under high H_2 pressure at several pH, and $[RuHCl(m\text{tppms})_3]$, $[\{RuHCl(m\text{tppms})_2\}_2]$ *cis*-$[Ru(H)_2(m\text{tppms})_4]$, *trans*-$[Ru(H)_2(m\text{tppms})_4]$, and $[RuH(H_2)\ (m\text{tppms})_4]^+$ were detected.

In a related attempt, water-soluble Ru(II) complexes with N-heterocyclic carbene ligands were synthetized [3] and used as catalysts of hydrogenation and redox isomerization reactions.

The support of COST (D29, Working Group 0009/3: Green Chemistry through Aqueous Organometallic Catalysis) as well as that of OTKA, Hungary (T043365) are gratefully acknowledged.

[1] F. Joó, J. Kovács, A. Cs. Bényei, Á. Kathó, *Angew. Chem. Int. Ed. Engl*. **1998**, *37*, 969.
[2] G. Papp, J. Elek, L.Nádasdi, G. Laurenczy, F. Joó, *Adv. Synth. Catal.* **2003**, *345*, 172.
[3] P. Csabai, F. Joó, *Organometallics* **2004**, *23*, 5640.

8

Artificial Metalloenzymes for Enantioselective Catalysis

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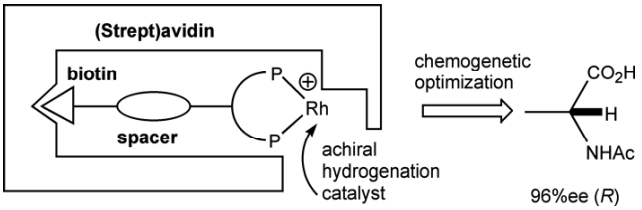
Homogeneous- and enzymatic catalysis offer complementary means to generate enantiomerically pure compounds. Incorporation of achiral biotinylated rhodium-diphosphine complexes into (strep)avidin yields artificial metalloenzymes for the hydrogenation of N-protected dehydroaminoacids (Scheme). A chemogenetic optimization procedure allows to produce both enantiomers of acetamidoalanine in good enantioselectivity (up to 96% ee). Analysis of the performance of these hybrid catalysts reveal features reminiscent both of enzymatic and of homogeneous systems. Our most recent results on artificial alcohol dehydrogenases will be presented as well.



Scheme. Artificial metalloenzymes for enantioselective hydrogenation reactions. The host protein (either avidin or streptavidin) displays a high affinity for the biotin anchor. Introduction of a spacer and variation of the ligand scaffold allows to chemically optimize the enantioselectivity. Fine tuning of the selectivity can be achieved via site-directed mutagenesis of the (strept)avidin.

9

Gadofullerenes and Gadonanotubes: Potential High-Performance MRI Contrast Agents

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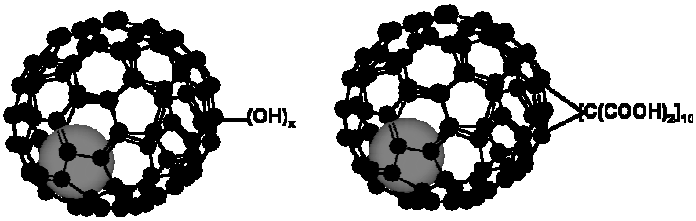
Contrast Agents (CAs) play a prominent role for magnetic resonance imaging in medicine: they are primarily used to improve disease detection by increasing sensitivity and diagnostic confidence. Annually approximatively sixty million MRI procedures are performed worldwide and around 30% of these procedures use MRI CAs. Currently, stable Gd^{3+} poly(aminocarboxylate) complexes are widely used as CAs in medicinal MRI.



Water-soluble gadofullerenes [1] and superparamagnetic gadonanotubes [2] have been suggested as CAs. Recent results will be presented.

[1] É. Tóth, R. D. Bolskar, A. Borel, G. González, L. Helm, A. E. Merbach, B. Sitharaman, L. J. Wilson, *J. Am. Chem. Soc.* **2005**, 127, 799.

[2] B. Sitharaman, K. Kissell, K. B. Hartman, L. Tran, A. Baikalov, I. Rusakova, Y. Sun, H. Khant, S. Ludtke, W. Chiu, S. Laus, É. Tóth, L. Helm, A. Merbach, L. Wilson, *Chem. Commun.* **2005**, *in press*

Action D15

10

Ultrafast Dynamics of Nonequilibrium Electrons in Metal/Adsorbates Nanosystems

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Faculté des Sciences de Base
Ecole Polytechnique Fédérale de Lausanne
CH-1015 Lausanne, Switzerland

A metal/adsorbates nanosystem has been prepared to explore the ultrafast behaviour of nonequilibrium electrons at metal/molecule interfaces. As a model, gold nanoparticles (NPs) with diameters of 1.7 to 9 nm wrapped in a shell of sulfate have been chosen to investigate the role of adsorbates on the dynamics of electron-electron and electron-phonon interaction processes by femtosecond pump-probe transient absorption and four-wave mixing spectroscopy. Broad-band transient absorption spectroscopy allows identifying the spectral response of nonthermal electrons with respect to the hot electron gas. Electron-electron scattering time constants are found to be slower in metal/adsorbates compared to bulk materials or naked gold NPs with similar sizes. Adsorbates provide an additional decay channel for nonthermal electrons, i. e. the ultrafast inelastic resonant tunneling into empty electronic states of adsorbates. The multiple cycles of excitation-deexcitation of adsorbates by electronic transitions induces a negative feedback. As a result, this phenomenon gives rise to nonlinear dynamics and to hot adsorbates bottleneck effects, which slow down the internal thermalization. Furthermore, the rates of e-e and e-ph interactions within the critical size range below 10 nm are size dependent, i. e. 500 fs to 1 ps for e-e scattering and 1 to 1.9 ps for e-ph coupling with decreasing nanosystem sizes. The same size behaviour trend observed for e-e and e-ph interactions is understood in terms of control of the average rate of phonon emission by the long-lived nonthermal regime induced by adsorbates.

Action D18

11

Phosphorus Containing Derivatives of DOTA: New Potential MRI Contrast Agents

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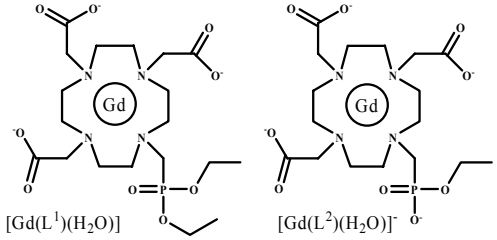
[b] Laboratoire de chimie inorganique et bioinorganique, Ecole Polytechnique Fédérale de Lausanne, CH-1015 Lausanne, Switzerland

Phosphorus analogues of DOTA are known to have interesting properties for the usage as potential MRI contrast agents. Their residence time of water in the inner sphere (τ_M) of Gd(III) complexes is much smaller than for $[Gd(DOTA)(H_2O)]^-$ and the presence of second sphere water molecules enhances the overall relaxivity [1].



$[Gd(L^1)(H_2O)]$ $[Gd(L^2)(H_2O)]^-$

We report the syntheses of two new phosphorus containing ligands and their lanthanide(III) complexes. Multinuclear NMR studies followed by simultaneous fitting show that τ_M is smaller than that of $[Gd(DOTA)(H_2O)]^-$. The relaxivities of complexes $[Gd(L^1)(H_2O)]$ and $[Gd(L^2)(H_2O)]^-$ are equal to 3.4 and 3.5 $mM^{-1}s^{-1}$, respectively (20 MHz, 37 °C, pH 6.5). The phosphonic function allows further functionalization of the ligands and the synthesis of targeting MRI contrast agents.

[1] J. Rudovský, P. Cígler, J. Kotek, P. Hermann, P. Vojtíšek, I. Lukeš, J. A. Peters, L. Van der Elst, R. Muller, *Chem. Eur. J.* **2005**, *11*, 1.

Action D18

12

Metallostars: Concentrating Relaxivity into a Small Molecular Space

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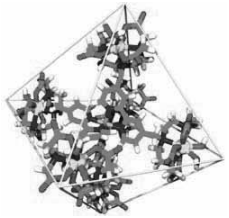
Laboratoire de Chimie Inorganique et Bioinorganique, Ecole Polytechnique Fédérale de Lausanne, EPFL-BCH, CH-1015 Lausanne, Switzerland

The development of a high relaxivity Gd(III) MRI contrast agent involves the fine-tuning of several determining parameters such as an optimal water exchange rate and a slow overall rotation of the thermodynamically stable Gd(III) complex. With this criteria in mind we have designed a novel heterotritopic ligand comprising a 2,2'-bipyridine moiety for specific Fe(II) binding and two poly(aminocarboxylate) groups for Gd(III) coordination [1]. The ligand self-assembles into a rigid metallostar bearing 6 paramagnetic Gd(III) around its core. The stability constants of the Gd(III) complexes formed with the ligand and the metallostar, an important factor for in vivo safety, as well as the protonation constants of the ligand, were determined by potentiometry. ^{17}O NMR and NMRD studies performed show that a water exchange rate is close to the optimal values and that the presence of two inner-sphere water molecules double the inner-sphere contribution to the relaxivity. Analysis of the longitudinal ^{17}O and ^1H relaxation rate data according to the Lipari-Szabo approach evidences the presence of internal flexibility.



[1] J. B. Livramento, É. Tóth, A. Sour, A. Borel, A. E. Merbach, R. Ruloff, *Angew. Chem. Int. Ed.* **2005**, *44*, 1480.

Action D18 **13**

Determination of the Zero Field Splitting parameters for several Gd(III) complexes in frozen solutions by high frequency EPR technique

Meriem Benmelouka,[a] Johan Van Tol,[b] Alain Borel,[a] Lothar Helm [a] and André. E Merbach [a]

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[b] National High Magnetic Field Laboratory, Center for Interdisciplinary Magnetic Resonance, Florida State University, Tallahassee, Florida, USA

The electronic spin relaxation of Gd(III)-based MRI contrast agents is one of the most important factors which determines the enhancement of water proton relaxation (*relaxivity)* and is currently the subject of both experimental and theoretical studies .
In the aim determining the influence of the electron relaxation on the relaxivity, multiple frequency and temperature EPR measurements on several Gd-complexes in solution have been performed.
A multifrequency EPR approach allows more accurate determination of the field-dependent (Zeeman contribution) and the field-independent components (the Static and the Transient Zero Field Splitting) of the electron spin Hamiltonian. In liquid solution we can only observe the effect of the ZFS parameters on relaxation. Thanks to the lack of molecular motions in frozen solutions, it is now possible to directly measure both the static and the transient ZFS.
Here we report the study by High Field EPR (240GHz) of glasses of Gd(III) complexes at several temperatures.
For the first time with that type of compounds, we are able to determine from these EPR data the average ZFS parameters and their distributions. Since the ZFS is related to the crystal field, our results constitute a first step towards establishing a relationship between molecular structure and the ZFS.

Action D18 **14**

Quantum Chemical Calculations of Basic NMR Parameters of Gd-based MRI Contrast Agents

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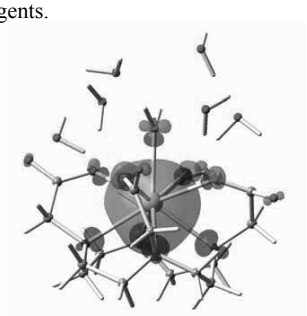
[b] Institute of Inorganic Chemistry, Slovak Academy of Sciences, SK-84536 Bratislava, Slovak Republic

A computational strategy based on density functional theory and classical molecular dynamics simulations was developed for accurate prediction of hyperfine and quadrupole coupling constants on the first coordination sphere water molecule of Gd-based magnetic resonance imaging (MRI) contrast agents. These properties are responsible for dipole-dipole and quadrupole mechanisms of nuclear relaxation. The results obtained will help to understand more deeply relaxation phenomena and to develop novel efficient MRI contrast agents.



Spin density map (±0.0005 a.u.$^{-3}$ isosurfaces) shows significant negative spin-polarization of first coordination sphere water molecule in GdDOTA.

Action D20 **15**

Artificial Metalloenzyme for the Enantioselective Reduction of Ketones by Transfer Hydrogenation

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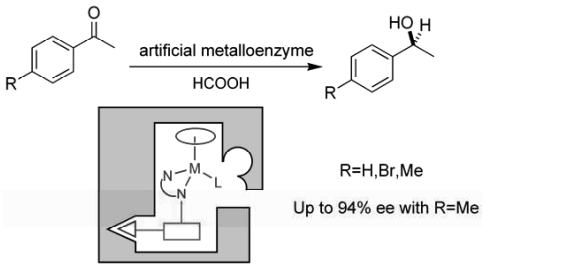
Homogenous- and enzymatic catalysis are in many respects complementary for the synthesis of enantiopure compounds. As the subtle details that govern chiral discrimination are difficult to predict, improving the performance of such catalysts often relies on trial-and-error procedures. Homogenous catalysts are optimized by chemical modification of the first coordination sphere and enzymes can be improved by modification of gene encoding the protein.
The supramolecular anchoring of a biotinylated organometallic catalyst into a host protein ((Strept)avidin) affords versatile artificial metalloenzymes for the reduction of ketones by transfer hydrogenation [1].



A combined chemo-genetic procedure to optimize the activity and the selectivity of the metalloenzyme will be presented.

[1] C. Letondor, N. Humbert, R. T. Ward, *Proc. Natl. Acad. Sci. USA.* **2005**, *102*, 4683.

Action D20 **16**

Nanobiotechnology: Discrete, One- and Two Dimensionnal Protein Arrays Triggered By Metal Coordination to Bis-Biotinylated Ligands Bound to Streptavidin

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Our group has recently been involved in the use of the biotin-avidin technology to produce efficient artificial metalloenzymes. For this purpose, a ligand is covalently linked to biotin, which when reacted to streptavidin, produces a supramolecular biotin⊂streptavidin complex which displays catalytic properties reminiscent both of enzymes and homogeneous catalysts.

In this study, the linker between the biotin anchor and the ligand is extended to ensure that the metal is located outside of the streptavidin host protein. With this method, and depending on the coordination properties of the transition metal, the {metal-ligand-biotin}⊂streptavidin building blocks can be assembled in various geometries. The resulting discrete, one- and two dimensionnal protein assemblies can be analyzed by atomic force microscopy, revealing well organized protein arrays, reminiscent of molecular tectonics.

[1] C. Letondor, N. Humbert, T. R. Ward, *Proc. Nat. Acad. Sci. USA.* **2005**, *102*, 4683.
[2] T. R. Ward, *Chem. Eur. J.* **2005**, *in press*.

Action D21 **17**

Binding of Pt(II) Anticancer Drugs to Zn_7Metallothionein: *Trans*-Complexes Retain Their Amine Ligands

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cis-$(NH_3)_2PtCl_2$ (*cis*-DDP) and other *cis*-L_2PtCl_2 (L, amine ligand) derivatives represent one of the most potent antitumor drugs. They exert their effects through binding to chromosomal DNA, which lead to cell-cycle arrest and apoptosis. However, the treatment of patients is often overshadowed by the development of drug resistance [1]. The reason for drug resistance, among others, is the metal detoxification through increased production of intracellular thiols, particularly metallothionein (MT) [2].

To gain insights into the role of MT in Pt^{II} resistance the reaction kinetics of Zn^{II} release and the formation of Pt^{II}-MT complexes were studied. The Zn^{II} release from human Zn^{II}_7MT-2 upon its reaction with several *cis*- and *trans*-Pt^{II} complexes was followed using the chelating dye 4-(2-pyridylazo)resor-cinol (PAR) at 500 nm. The results showed that *trans*-L_2PtCl_2 compounds displace Zn^{II} much faster compared to *cis*-L_2PtCl_2. The same behavior was also observed when the formation of CysS → Pt^{II} LMCT band was followed at 285 nm. To further characterize the nature of the final products nano-ESI-MS was employed for the first time. The MS analysis of Pt^{II}-MT complexes revealed that while in the reaction with *cis*-L_2PtCl_2 all ligands were displaced by protein thiolates, in that with *trans*-L_2PtCl_2 both L were retained even after several days due to the *trans*-effect of sulfur. Thus, *trans*-Pt^{II} in complex with the protein remained in a potentially active form. These results are important for the rational design of new Pt^{II} drugs and show for the first time that MT may act as a Pt^{II} reservoir and/or shuttle to DNA for recently developed antitumor *trans*-Pt^{II} compounds.

[1] D. Wang, S. J. Lippard, *Nat. Rev. Drug Discov.* **2005**, *4*, 307.
[2] J. K.-C. Lau, D. V. Deubel, *Chem. Eur. J.* **2005**, *11*, 2849.

Action D21 **18**

Reactions of Human and Plant Hemoglobins with Nitrogen Monoxide and Peroxynitrite

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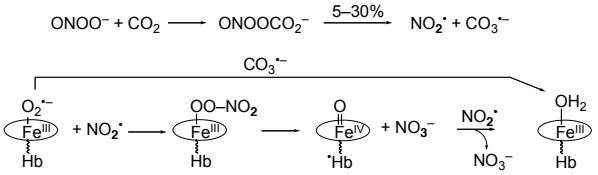
Metalloproteins, in particular hemoproteins, have been shown to interact with nitrogen monoxide and peroxynitrite in a variety of different ways, depending on the structure of the proteins and on the oxidation state of the metal center. Here we present our studies of the reactions of peroxynitrite with the iron(III)- and the oxy-forms of human hemoglobin (Hb) and of soybean leghemoglobin (Lb), in the presence and absence of CO_2.

Kinetic studies by stopped-flow spectroscopy showed that, in the presence of physiologically relevant amounts of CO_2, the reaction of oxyHb with peroxynitrite proceeds according to the following scheme [1]:



Preliminary results suggest that the reaction of oxyLb with peroxynitrite proceeds also in two steps.

Stopped-flow spectroscopic studies showed that both metHb and metLb catalyze the isomerization of peroxynitrite to nitrate. The values of k_{cat} obtained for metHb and metLb at 20 ºC are $(3.9 \pm 0.2) \times 10^4$ M^{-1} s^{-1} (pH 7.0) and $(1.45 \pm 0.02) \times 10^5$ M^{-1} s^{-1} (pH 7.3), respectively. The physiological relevance of these reactions will be discussed.

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Action D21 **19**

Nitrogen Monoxide Reacts and the Glutathione Thiyl Radical – A Kinetc Study

Dustin Hofstetter, Thomas Nauser, Willem H. Koppenol

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S-nitrosoglutathione (GSNO) is a vasodilator and has numerous other biologial functions [1]. It's biosynthesis is proposed to involve the reaction of nitrogen monoxide ($NO^•$) with the glutathione thiyl radical ($GS^•$). Therefore the reaction $GS^• + NO^• \rightarrow$ GSNO (reaction 1) was studied under various conditions.

The laser flash photolysis at 266 nm of GSNO in $NO^•$-saturated water lead to $GS^• + NO^•$. Their recombination with a rate constant $k1 \leq 6.3 \cdot 10^6$ M^{-1} s^{-1} was not quantitative. The laser flash photolysis at 266 nm of oxidized glutathione (GSSG) in $NO^•$-saturated water did not show any substantial formation of GSNO at its characteristic absorption at 530 nm. With pulse radiolytic reduction of GSH by $H^•/e^-_{aq}$ in 95% $NO^•$ saturated water a rate constant of $k_1 \approx 2 \cdot 10^7$ M^{-1} s^{-1} was determined. These results and the low bioavailable concentrations of the participating species indicate that the radical formation pathway is not probable: $[NO^•] \leq 10^{-7}$ M, decay of $GS^•$ by intramolecular $H^•$ transfer is faster than 10^3 s^{-1} [2]. Under such conditions, the yield of $GS^• + NO^•$ is less than 1%.

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[2] L. Grierson, *Int. J. Radiat. Biol.* **1992**, *62*, 265

Action D24 **20**

o-Hydroxy-α-alkylbenzylamines: Building Blocks for New Chiral Ligands

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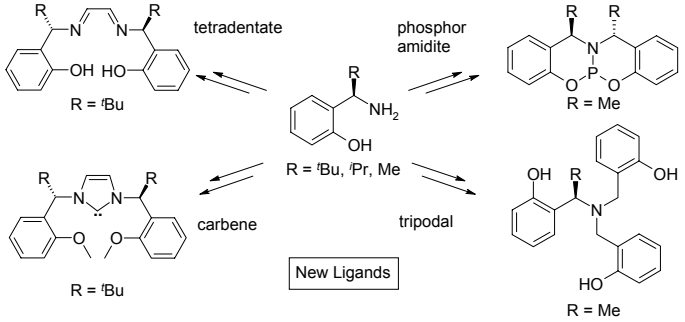
Although being important constituents of several antibiotics and other biologically active natural products, 1,3-aminoalcohols have not seen extensive use as chiral auxiliaries or ligands. Therefore, starting from the building block *o*-hydroxy-α-alkyl-benzylamine [1][2], a number of new mono- to tetra-dentate chiral ligands have been synthesized. Several asymmetric catalytic reactions are envisaged: epoxidation (tetradentate ligands), hydrosilylation or Heck reaction (phosphoramidites, carbenes), Lewis acid catalysed aza-Diels-Alder (tripodal ligands) and alkene metathesis (carbenes). Preliminary investigations in complex formation and in asymmetric catalysis will be discussed.



[1] E. P. Kündig, C. Botuha, G. Lemercier, P. Romanens, L. Saudan, S. Thibault, *Helv. Chim. Acta* **2004**, *87*, 561.
[2] G. Bernardinelli, D. Fernandez, R. Gosmini, P. Meier, A. Ripa, P. Schupfer, B. Treptow, E. P. Kündig, *Chirality* **2000**, *12*, 529.

Action D24 **21**

Effective Stereocontrol of Chiral Piano-Stool Metal Complex Geometry by a Coordinating Enantiopure Counterion

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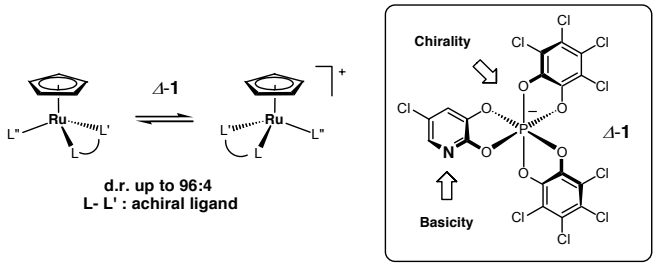
Cationic cyclopentadienyl ruthenium(II) complexes are chiral if four different ligands surround the pseudo-tetrahedral metal atom. These derivatives are configurationally labile and enantiopure bidentate ligands are typically used to control the configuration of the metal center; chiral monodentate or Cp equivalents being usually less efficient for the stereocontrol [1].



We now report the synthesis and resolution of a novel hexacoordinated phosphate anion **1** (*Λ* or *Δ* enantiomer) that exhibits not only counterionic but also *Lewis* basic capacities [2]. This monodentate anion displays unprecedented level of stereocontrol of piano-stool metal complex geometry (d.r. up to 96:4).

[1] H. Brunner *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 1194; C. Ganter, *Chem. Soc. Rev.* **2003**, *32*, 130.
[2] J. Lacour, R. Frantz, *Org. Biomol. Chem.* **2005**, *3*, 15; S. Constant, J. Lacour, *Top. Curr. Chem.* **2005**, *250*, 1.

Action D25 **22**

Cyanodeoxy-Glycosyl Derivatives as Substrates for Enzymatic Reactions

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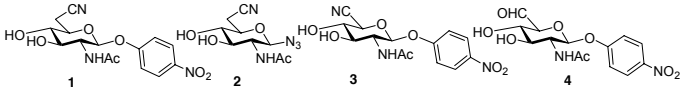
[a] Dept. Organic Chemistry, Faculty of Chemistry, University of Seville, Spain; [b] Institute of Microbiology, Laboratory of Biotransformation, Academy of Sciences of the Czech Republic, Prague 4,Czech Republic; [c] Laboratory of High Performance Computing, Institute of Physical Biology USB and Institute of Landscape Ecology AS CR, Nové Hrady, Czech Republic.

In the synthesis of complex carbohydrate structures, enzymatic methods using glycosidases are successfully applied [1]. The main requirement for their substrates is the presence of a good leaving group – besides nitrophenyl glycosides, glycosyl azides [2] have recently been demonstrated as efficient substrates. Glycosidases accept structurally modified substrates, which enable to investigate different aspects of their substrate specificity.
We present the synthesis of nitriles **1**, **2**, **3** and 6-carbaldehyde **4** and their potential as substrates of glycosidases and nitrilases and inhibitors of glycosidases.



We also present molecular modeling and docking of the respective compounds into the active site of the β-*N*-acetylhexosaminidase from *A. oryzae* that revealed interaction energy comparable with the natural substrate suggesting a strong binding into the active site.

[1] J. Zhang, J. Shao, P. Kowal, P. G.Wang, *Carbohydrate-Based Drug Discovery* **2003**, *1*, 137.
[2] P. .Fialová, A. T. Carmona, I. Robina, R. Ettrich, P. Sedmera, V. Přikrylová, L. Hušáková, V. Křen, *ChemBiochem* sent for publication

Action D25 **23**

Artificial Metalloenzymes: (Strept)Avidin as Host for Enantioselective Hydrogenation

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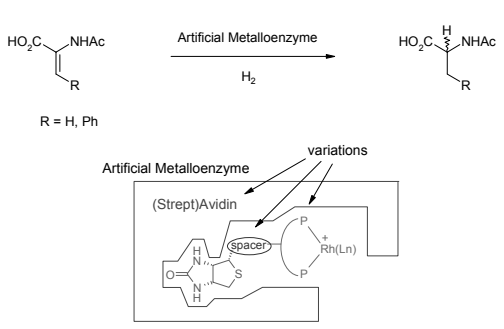
Incorporation of achiral, biotinylated aminodiphosphine–rhodium complexes in (strept)avidin affords catalysts for the enantioselective hydrogenation of enamides [1]. A chemogenetic optimization procedure allows the optimization of the enantioselectivity for the reduction of prochiral enamides in up to 96 % ee. The influence of the nature of the spacer, diarylphosphine residue, guest protein and solvent on activity and selectivity will be presented. Such artificial metalloenzymes based on the biotin–avidin technology display features that are reminiscent of both homogeneous and of enzymatic catalysis.



[1] M. Skander, N. Humbert, J. Collot, J. Gradinaru, G. Klein, A. Loosli, J. Sauser, A. Zocchi, F. Gilardoni, T. R. Ward, *J. Am. Chem. Soc.* **2004**, *126*, 14411.

Action D26 **24**

Theoretical Studies on the Electronic Properties and the Chemical Bonding of Transition Metal Complexes using DFT and Ligand Field Theory

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[a] Departement de Chimie, Université de Fribourg, Fribourg, Swizterland; [b] Institute of General and Inorganic Chemistry, Bulgarian Academy of Sciences, Sofia, Bulgaria; [c] Anorganisch-Chemisches Institut, Ruprecht-Karls-Universität Heidelberg, Heidelberg, Germany

In this presentation, we give a brief outline of a recently proposed approach for modeling ground and excited state electronic properties of transition metal complexes. It is based on a combination of Ligand Field theory, which is a classical tool for interpretation and modern density functional theory and it is shown that the new approach is equally suitable both for single nuclear [1,2] and poly-nuclear transition metal complexes [3-4]. While ab-initio methods, such as multi reference CI have been applied with success to model ground and excited state properties of single nuclear complexes, magnetic exchange coupling still presents a challenge for ab-initio based methods. A parameterization of the ligand field for oligonuclear transition metal complexes allows to circumvent the size problem for calculating the exchange coupling constants and the magnetic properties, thus having a big impact for applications in molecular magnetism. In this talk a series of applications and test examples of magnetic exchange integrals will be given using experimentally well documented magnetic dinuclear complexes; these include bis-μ-hydroxo-bridged dimers of Cu(II) and oligonuclear cyanometallates. The impact of this approach will be discussed in close connection with ongoing experimental studies on these systems.

[1] M. Atanasov, C. A. Daul and C. Rauzy, *Chem.Phys.Lett.* **2003**, *367*, 737.
[2] M. Atanasov, C. A. Daul, C. Rauzy, *Struct. Bonding* **2004** *106*, 97.
[3] M. Atanasov, C. A. Daul, *Chem.Phys.Lett.* **2003**, *379*, 209.
[4] M. Atanasov, C. A. Daul, *Chem.Phys.Lett.* **2003**, *381*, 584.

Action D27 **25**

Vesicle Compartments from Prebiotically Relevant Amphiphiles

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[1] ETH, Department of Materials, Wolfgang-Pauli-Strasse 10, 8093 Zürich, Switzerland; [2] Rudjer Bošković Institute, Department of Physical Chemistry, Bijenicka c. 54, 10002 Zagreb, Croatia; [3] Jožef Stefan Institute, EPR-Center, Jamova 39, 10001 Ljubljana, Slovenia; [4] University of Ljubljana, Faculty of Pharmacy, Aškerčeva ulica 7, 1000 Ljubljana, Slovenia; [5] University of Bradford, School of Pharmacy, Bradford BD7 1DP, UK.

Vesicles are considered as reasonable models of protocells, the precursor structures of the first cells that may have appeared during the prebiological evolution [1,2]. Short-chain fatty acids belong to the bilayer-forming amphiphiles that may have been present on the early Earth [1], since they are chemically simple and since they have been found in carbonaceous meteorites [3]. By using different experimental techniques, the aggregation behavior of dilute aqueous dispersions of fatty acids (mainly decanoic acid) has been investigated, focusing particularly on the formation and properties of vesicles. The techniques used include electron microscopy, differential scanning calorimetry and electron paramagnetic resonance spectroscopy (using nitroxide labeled spin probes).
Vesicle formation in the case of decanoic acid is limited to a pH range between 6.8 and 7.8, the vesicles being always present in equilibrium with non-associated decanoate (about 10-20 mM). For vesicle formation at lower pH, sodium dodecylbenzenesulfonate can be added at equimolar amounts.

[1] D. W. Deamer, *Microbiol. Mol. Biol. Rev.* **1997**, *61*, 239.
[2] P. L. Luisi, P. Walde, T. Oberholzer, *Curr. Opin. Colloid Interf. Sci.* **1999**, *4*, 33.
[3] A. Shimoyama, H. Naraoka, M. Komiya, K. Harada, *Geochem. J.* **1989**, *23*, 181.

Action D28 **26**

Total Diastereoselective Synthesis of Substituted Pyrrolidines

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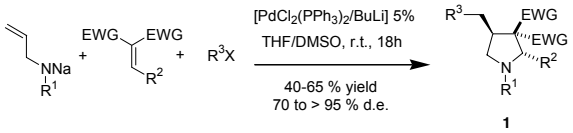
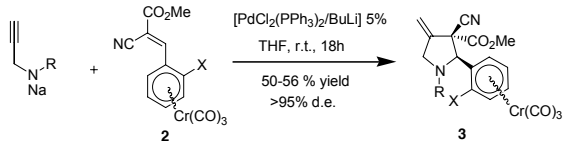
[a] Laboratoire de Chimie Organique 1, Université Claude Bernard Lyon 1, F-69622 Villeurbanne; [b] Department of Organic Chemistry, University of Geneva, CH-1211 Geneva

As part of our ongoing research aimed at the development of transition metal-mediated, multicomponent, five-membered heterocycle syntheses, we recently described a diastereoselective synthesis of highly substituted pyrrolidines (**1**) [1].



1

We have now found that the selectivity of a related one-pot palladium-catalysed reaction can be increased by coordinating the arene to a bulky chromium tricarbonyl fragment (**3**).



2 **3**

This also offers opportunities in asymmetric synthesis via an enantiopure planar chiral complex **2**.

[1] L. Martinon, S. Azoulay, N. Monteiro, G. Balme, E. P. Kündig *J. Organomet. Chem.* **2004**, *689*, 3831

Action D28 **27**

A New Type of Schmidt Rearrangement: Towards the Asymmetric Total Synthesis of (-)-Indolizidine 167B

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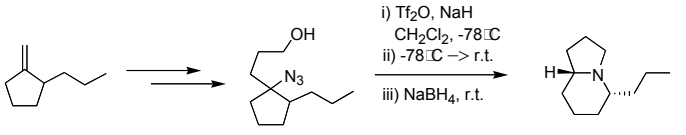
Universität Bern, Departement für Chemie und Biochemie, Freiestrasse 3, CH-3012 Bern, Switzerland

Azidoalcohol **2** is readily available as a 1:1 mixture of diastereomers in 2 steps from terminal olefin **1** via radical carboazidation [1] and subsequent reduction. Triflation and warming up leads to a spontaneous Schmidt type rearrangement [2] to the imminium salt which is then stereoselectively reduced to obtain racemic Indolizidine 167B **3**. This result represents the first example of a Schmidt rearrangement initiated by a nucleophilic substitution onto a primary carbon center. Regioselectivity problems of the rearrangement originating from the diastereomeric mixture of **2** will be discussed.



1 **2** **3**
(±)-Indolizidine 167B

Currently we are working on the asymmetric synthesis of **3**. We expect that the configuration of the chiral center α to the olefin doesn't epimerize during the rearrangement, so it should be possible to obtain natural (-)-Indolizidine 167B by starting from optically pure **2**.

[1] P. Panchaud, L. Chabaud, Y. Landais, C. Ollivier, P. Renaud, S. Zigmantas, *Chem. Eur. J.* **2004**, *10*, 3606
[2] W. H. Pearson, R. Walavalkar, J. M. Schkeryantz, W.-K. Fang, J. D. Blickensdorf, *J. Am. Chem. Soc*. **1993**, *115*, 10183

Action D28 **28**

The Total Synthesis of (–)-Lepadiformine

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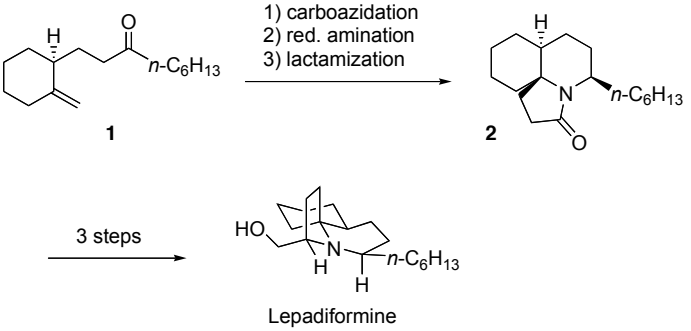
Lepadiformine is a marine alkaloid from *Clavelina lepadiformis* with a unique tricyclic structure, which displays interesting cytotoxic activities and cardiovascular effects [1]. By using the radical carboazidation developed in our group [2], we provided a particularly short synthetic route to lepadiformine and a series of other alkaloids. Thus, the carboazidation of optically pure olefin **1** followed by two cyclizations gave tricyclic lactam **2**, which was further elaborated to give (–)-lepadiformine.



1 **2**

Lepadiformine

[1] M. Jugé, N. Grimaud, J.-F. Biard, M.-P. Sauviat, M. Nabil, J.-F.Verbist, J.-Y. Petit, *Toxicon* **2001**, *39*, 1231.
[2] P. Panchaud, L. Chabaud, Y. Landais, C. Ollivier, P. Renaud, S. Zigmantas, *Chem. Eur. J.* **2004**, *10*, 3606.

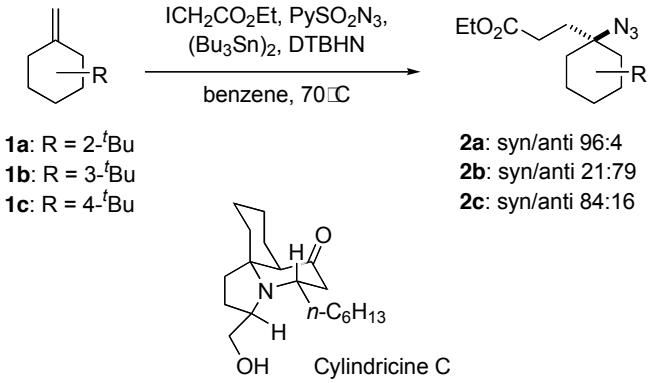
Action D28 **29**

Investigations into the Diastereoselectivity of the Radical Carboazidation

Pascal Schär, Sylvaine Cren and Philippe Renaud

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

While applying the radical carboazidation [1], to the total synthesis of various natural products, we were confronted with low diastereoselectivities during its course. Investigations on conformationally restricted model systems **1a** – **1c** revealed a preference for axial attack of the azide moiety. In the case of **1a**, a very high diastereomeric ratio was obtained most probably due to pyramidalization of the intermediate radical. We are currently looking into ways to implement these findings for the improved synthesis of natural products like cylindricine C.



[1] P. Panchaud, L. Chabaud, Y. Landais, C. Ollivier, P. Renaud, S. Zigmantas, *Chem. Eur. J.* **2004**, *10*, 3606.

Action D28 **30**

A Novel Strategy for the Synthesis of Optically Pure of *Cephalotaxus* Alkaloids

Monica G. Gonçalves Martin, Sarunas Zigmantas and Philippe Renaud

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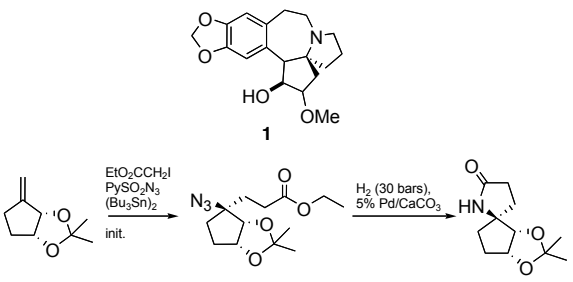
Recently our group has developed a procedure for one-pot intermolecular radical addition [1]. To study the control of the relative and absolute stereochemistry of the spirocenter we decided to synthesise cephalotaxine **1**.



The spirocenter of cephalotaxine is stereogenic and the control of its absolute configuration is a key feature. To achieve this stereocontrol we are working with bicyclic compounds.

[1] P. Renaud, C. Ollivier, P. Panchaud, *Angew. Chem. Int. Ed.* **2002**, 41, 3460

Action D28 **31**

Asymmetric Total Synthesis of Fragments of Rifamycin S and Baconipyrones

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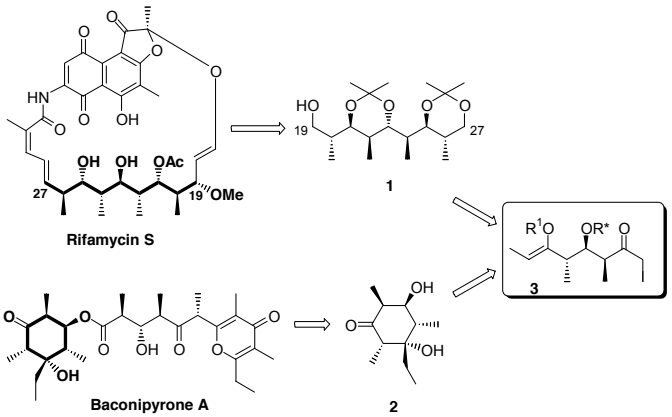
Laboratoire de glycochimie et de synthèse asymétrique, Ecole Polytechnique Fédérale de Lausanne, BCH, 1015 Lausanne, Switzerland

We would like to report here formal total synthesis of Rifamycin S and the first asymmetric synthesis of cyclohexanone subunit of Baconipyrones A and B (**2**). The key intermediate in our approach is stereotriad **3** which results from recently reported Vogel's oxyallylation reaction cascade on enantiomerically enriched 1-alkoxy-3-acyloxy-1,3-dienes [1],[2].



[1] M. Turks, X. Huang, P. Vogel, *Chem. Eur. J.* **2005**, *11*, 465.
[2] M. Turks, M. C. Murcia, P. Vogel, *Org. Lett.* **2004**, *6*, 3031.

Action D29 **32**

Kinetics and Mechanism of Catalytic CO_2/HCO_3^- Reduction in Water/Ionic Liquid using [{$RuCl_2$(*m*tppms)$_2$}$_2$] Precursor

Gábor Papp,[a] Ferenc Joó,[b] Gábor Laurenczy[c]

[a]Res. Group of Homog. Catal., H.A.S., Debrecen, Hungary, [b]Dept. of Phys. Chem., Univ. Debrecen, Hungary, [c]EPFL, ISIC, Lausanne, Switzerland

Several attempts have already been made to reduce HCO_3^-, CO_2 and carbonates into formate [1-3]. In this contribution we present some of our results on the catalytic hydrogenation of CO_2 and carbonates in ionic liquid and in aqueous solution. The hydrogenation of sodium bicarbonate in butyl-methyl-imidazolium-tetrafluoro-borate ionic liquid, in water free system, can not be carried out, as the $NaHCO_3$ is insoluble in this ionic liquid. Giving 10% D_2O into the IL, the sodium-bicarbonate can be dissolved, so the reduction has been studied under 100 bar H_2 pressure, using [{$RuCl_2$(mtppms)$_2$}$_2$] catalyst: formation of sodium formate has been detected (TOF = 3.05 h^{-1}). The [{$RuCl_2$(mtppms)$_2$}$_2$] complex also catalyses the H-D exchange in these systems, and 60 % of all formate is present as $D^{13}COO^-$, corresponding to the initial D/H ratio in the samples. The H/D exchange being faster than the hydrogenation [4-5], this H/D ratio does not change during the reduction.

Acknowledgement. Swiss State Secretariat for Education and Research (SER) and COST–ESF are thanked for financial support.

[1] F. Joó, G. Laurenczy, L. Nádasdi, J. Elek, *Chem. Commun.* **1999**, 971.
[2] G. Laurenczy, F. Joó, L. Nádasdi, *High Pressure Res.* **2000**, *18*, 251.
[3] G. Laurenczy, F. Joó, L. Nádasdi, *Inorg. Chem.* **2000**, *39*, 5083.
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[5] G. Kovács, L. Nádasdi, F. Joó, G. Laurenczy, *Green Chem*. **2003**, *5*, 213.

Action D29 **33**

Catalytic CO_2 Reduction in Aqueous Solution using $CpRu(PTA)_2Cl$ and $Cp^*Ru(PTA)_2Cl$ Precursors

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[a]EPFL, ISIC, Lausanne, [b]ICCOM CNR, Sesto Fiorentino (Firenze), Italy

The use of CO_2, limestone and other carbonates, as C_1 building blocks is a major challenge for chemistry. The reduction of CO_2 to formic acid derivatives were reported using platinum metal group based catalysts [1]. Interest in the half sandwich ruthenium(II) water soluble complexes has increased over the past few years due to potential applications [2]. The water soluble complexes $CpRu(PTA)_2Cl$ (**1**) and $Cp^*Ru(PTA)_2Cl$ (**2**) are known to hydrogenate C=C moieties selectively under biphasic conditions [3], it was shown that (**2**) forms the dihydride complex $[Cp^*Ru(H)_2(PTA)_2]Cl$ under 30 bar H_2 at 50°C, whereas the monohydride is the only species formed from **1**. We have studied the catalytic activity of these water soluble complexes **1** and **2** in the aqueous reduction (up to 100 bar H_2 pressure) of $CO_3^{2-}/HCO_3^-/CO_2$ into formate, as a function of pH, over the temperature range 30-80°C. It has been shown that both **1** and **2** are catalysing the hydrogenation reaction, however **2** was found to be more active. In general, at higher pH values lower turnover frequencies were observed for both **1** and **2**. Although the hydride species, generally active in reduction, for **1** and **2** have been formed under H_2 pressure, in presence of substrate we could not observed the corresponding specific signals by ^1H NMR.

Acknowledgement. Swiss State Secretariat for Education and Research (SER), COST–ESF and EC through project HPRN-CT-2002-00176 are thanked for financial support.

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Action D30 **34**

High Pressure FT-IR Studies on Catalytic Alkene Hydroformylation

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High pressure techniques have been proven to be useful tools for *in situ* mechanistic investigations of catalytic hydroformylation reactions [1-3]. Hydroformylation is a well known synthetic tool for the preparation of a wide range of organic molecules of high commercial value, one of the most important applications of homogeneous catalysis in an industrial process for the manufacture of alcohols [4]. Catalytic hydroformylations of olefins have been investigated *in situ* in a high pressure FT infrared cell using $RhH(CO)(PPh_3)_3$ catalyst. Different mechanisms have been observed in case of terminal (hex-1-ene) and in case of internal (cyclohexene) alkenes. During the hex-1-ene hydroformylation, acylrhodium complexes are present in important concentration, showing that the hydrogenolysis of the acylrhodium complexes is the rate determining step. Using cyclohexene as substrate, the presence of $RhH(CO)_2(PPh_3)_2$ has been detected, the slowest step of the catalytic cycle is its reaction with cyclohexene.

Acknowledgement. Swiss State Secretariat for Education and Research (SER) and COST–ESF are thanked for financial support.

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Action D31 **35**

A Chemosensor Array for the Colorimetric Identification of 20 Natural Amino Acids

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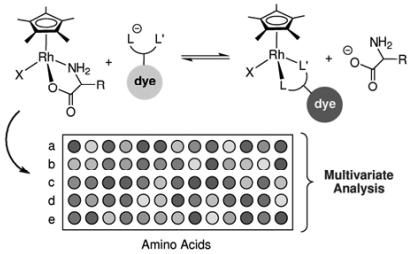
A synthetic receptor, which is bound via non-covalent interactions to an indicator, is able to function as a chemosensor [1]. The combination of several non-specific chemosensors comprises a sensor array [2]. In the following we describe a sensor array in which the respective sensors are assembled from commercially available building blocks at different pH. This array allows the differentiation of 20 natural amino acids with high fidelity using UV/vis spectroscopy in combination with multivariate analysis [3].



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Action D31 **36**

Different Ways to Program Metallo-organic Self-assembly

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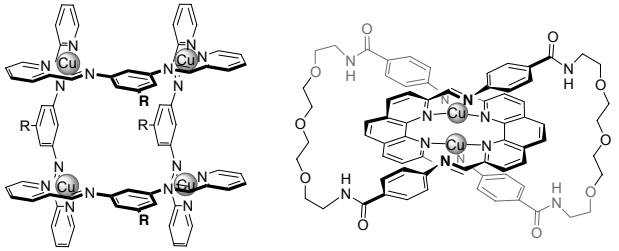
The goal of our research is to discover new means of controlling self-assembly phenomena, with the ultimate objective of developing functional self-assembled systems, i.e. molecular machines. The study of how supramolecular systems encode the information necessary for the self-assembly process to occur lies at the heart of our research program.

The use of aqueous copper(I) as an imine self-assembly template is a central feature of our chemistry [1]. Although neither Cu^I nor imines are ordinarily stable in water, they were demonstrated to mutually stabilize each other, allowing the formation of grids [2] and catenanes (shown below), as well as numerous other structures [3]. The stereochemistry and substitution reactions of these complexes may be controlled, as will be discussed.



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Action D31 **37**

Synthesis of Tetra-TTF-annulated Phthalocyanines: Potential Applications as One-dimensional Conductors within a Liquid-crystalline Phase

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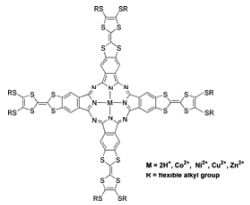
[a] Departement für Chemie und Biochemie, Universität Bern, Freiestrasse 3, CH-3012 Bern, Switzerland
[b] Laboratoire de Chimie, Ingénierie Moléculaire et Matériaux d'Angers, UMR CNRS 6200, 2 Bd Lavoisier, 49045 Angers, France

Phthalocyanines (Pcs) have been the subject of intense studies as a consequence of their wide range of coordination, optical, structural and electronic properties arising from their large π-conjugated system and their assembling into cofacially-stacked arrays.[1] The covalent linking of the Pc core with TTF units could produce an intriguing donor-Pc dyad system, which is expected to show efficient electron transfer from the donor to the Pc core. The synthesis of TTF-annulated Pcs has been successfully achieved in our group.[2] On this basis, by varying properly the peripheral R-groups, we intend to obtain a columnar discotic mesophase, revealing one-dimensional conductivity.



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Action D31 **38**

Interionic Supramolecular Stereocontrol of Configurationally Labile Tris(eilatin) Iron(II) Complex

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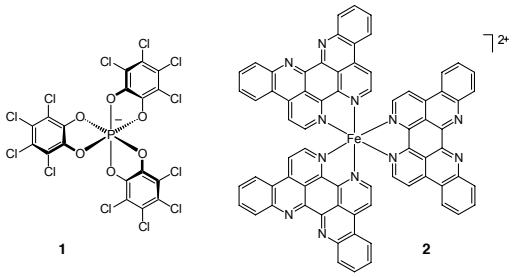
[b] School of Chemistry, Tel Aviv University, Israel

Previously, enantiopure TRISPHAT anion **1** has been shown to be a valuable chiral NMR solvating, resolving and asymmetry-inducing reagent for cationic chiral metallo-organic and organometallic complexes [1]. When associated with configurationally labile tris(diimine)iron(II) complexes, two anions **1** control the *Δ* or *Λ* configuration of the cationic propellers with selectivity up to or higher than 49:1. The sense of the induction strongly depends on the backbone of the ligands [2].



Herein we report the association of Δ-**1** and Λ-**1** with the tris(eilatin) iron(II) complex **2** that demonstrates high level of stereocontrol in even polar media; the salts displaying furthermore unusual CD spectra.

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Action D31 **39**

Triarylmethylphosphonium Cations: Supramolecular Stereocontrol and Exact Racemization Mechanism

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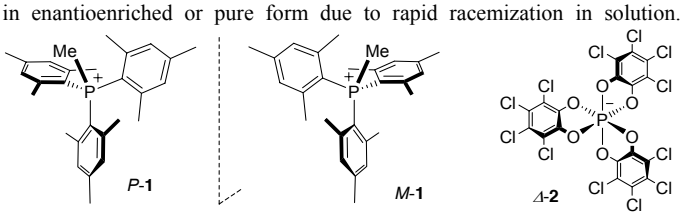
Triarylphosphines, their metal complexes, and triarylalkylphosphonium salts adopt, in solution and in the solid-state, chiral three-bladed propeller geometries that differ in the sense of twist of their aromatic rings, clockwise or counterclockwise with *P* and *M* configurations respectively [1]. So far, no such triarylphosphines and triarylalkylphosphonium salts have been isolated in enantioenriched or pure form due to rapid racemization in solution.



Herein, we report that the ion pairing of trimesitylmethylphosphonium **1**,[2] or triphenylmethylphosphonium cations with enantiopure hexacoordinated phosphorus anions, *e.g.* TRISPHAT **2**,[3] leads to a supramolecular stereocontrol from the anion onto the cation in solution (up to 47% d.e.) and in the solid state (100% d.e.). The presence of the chiral counterion allows furthermore the determination of the exact racemization mechanism (two-ring flip) by direct comparison of the rate of diastereotopic exchange and the one of racemization.

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Action D34 **40**

Different Approaches for Stereoselective Synthese of 2-Benzymidazolyl-3,4-dihydroxy-5-methylpyrrolidines. Evaluation of the Inhibitory Activity Toward Glycosidases.

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[a] Departamento de Química Orgánica de la Facultad de Química, Universidad de Sevilla, Aptdo. 553, Sevilla (Spain); [b] Laboratoire de Glycochimie et de Synthèse Asymétrique, BCH-EPFL, 1015-Lausanne-Dorigny

We have developed a new method for the preparation of (2*S*,3*S*,4*R*,5*S* and 5*R*)-5-methylpyrrolidine-3,4-diol derivatives bearing either benzimidazolyl (**2**) or phenyl (**3**) moieties, through carbaldehyde **1** that has been prepared stereoselectively starting from D-mannose. These compounds are selective and strong inhibitors of α-L-fucosidases. By comparing the enzymatic inhibition activity of **2** and **3** with diamine **4**, we have proved that aromatic moieties attached to the iminosugar backbone enhance the activity and specificity of the inhibitor, probably due to the establishment of hydrophobic interactions with the rim of the enzyme active site [1,2]. Furthermore, the presence of lipophilic groups satisfies the condition of membrane permeability required for a compound to become a useful drug [3].

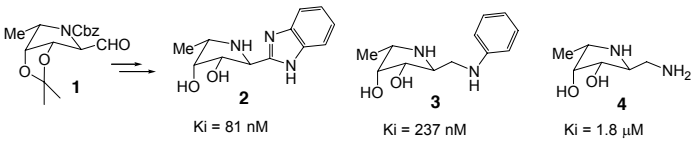

Figure1: New strong and selective α-L-fucosidase inhibitors

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Action D34 **41**

Synthesis of Trivalent Glycoconjugate Clusters as CD4 Binding Pocket Mimetics

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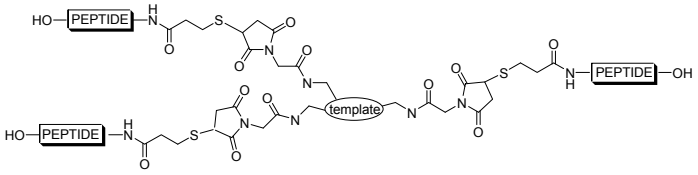
[a] Dept. Organic Chemistry, Faculty of Chemistry, University of Seville, P.O. Box 553, E-41071 Seville, Spain; [b] Dept. Organic and Pharmaceutical Chemistry, Faculty of Pharmacy, University of Seville, Spain.

Polyvalent interactions between glycoconjugates and receptors play a very important role in biological systems [1]. Based on the trimeric structure of gp120 complex [2], we present the synthesis of potential CD4 binding pocket mimetics by the use of different C3-symmetric templates to which different synthetic aminoacids (AAs), peptides or glycopeptides, can be attached separated by appropriate spacers.



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Action D34 **42**

Synthesis of 3,4-Dihydroxy-5-hydroxymethylprolines as New Scaffolds for the Incorporation into Peptidomimetics

Antonio J. Moreno-Vargas,[a] Inmaculada Robina[b] and Pierre Vogel[a]

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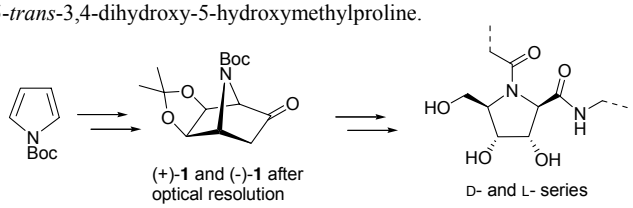
Enantiomerically pure (-)- and (+)-7-azabicyclo[2.2.1]hept-2-one derivatives (-)-**1** and (+)-**1** have been obtained from the Diels-Alder adduct of *N*-(*tert*-butoxycarbonyl)pyrrole and 2-bromo-1-(*p*-toluenesulfonyl)acetylene [1]. The synthetic route includes the Alexakis optical resolution [2] of ketone (±)-**1** via formation of cyclic aminals with (1*R*,2*R*)-diphenylethylenediamine. Compounds (-)-**1** and (+)-**1** were converted into *D*- and *L*-2,3-*trans*-3,4-*cis*-4,5-*trans*-*N*-(*tert*-butoxycarbonyl)-5-hydroxymethyl-3,4-isopropylidene-dioxyprolines, respectively. By applying the Boc and Fmoc strategies of peptide synthesis these compounds were used to construct two tripeptides containing the *D*- or *L*-2,3-*trans*-3,4-*cis*-4,5-*trans*-3,4-dihydroxy-5-hydroxymethylproline.



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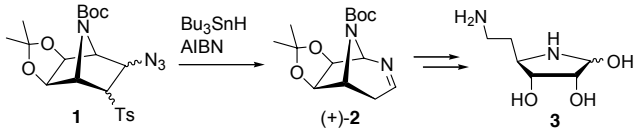
Action D34 **43**

Regioselective Rearrangement of 7-azabicyclo[2.2.1]hept-2-aminyl Radicals: An Approach to the Synthesis of 5-(2-aminoethyl)-2,3,4-trihydroxypyrrolidines, New Inhibitors of α-Mannosidases

Antonio J. Moreno-Vargas and Pierre Vogel

Laboratoire de Glycochimie et de Synthèse Asymétrique de l'Ecole Polytechnique Fédérale de Lausanne, BCH-EPFL, 1015-Lausanne-Dorigny

Enantiomerically pure 2,8-diazabicyclo[3.2.1]oct-2-ene derivatives (+)-**2** and (-)-**2** have been obtained from 2-azido-3-tosyl-7-azabicyclo[2.2.1]heptanes **1** and their enantiomers [1], by ring opening expansion under radical conditions. Compounds (+)-**2** and (-)-**2** were transformed into hemiaminals **3** and *ent*-**3** that showed good inhibition towards α-mannosidases (K_i = 0.9-2.5 μM).



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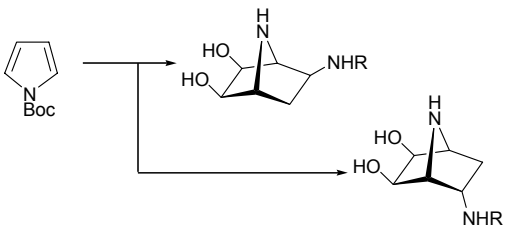
Action D34 **44**

Synthesis of Enantiomerically Pure Diamines Derivatives of 7-Azabicyclo[2.2.1]heptane. New Leads as Glycosidase Inhibitors and Rigid Scaffolds for the Preparation of Peptide Analogues

Antonio J. Moreno-Vargas and Pierre Vogel

Laboratoire de Glycochimie et de Synthèse Asymétrique de l'Ecole Polytechnique Fédérale de Lausanne, BCH-EPFL, 1015-Lausanne-Dorigny

The search for better inhibitors implies the multi-step synthesis of a large number of analogs and derivatives and their individual testing. Vogel and coworkers invented an efficient combinatorial method for the discovery of glycosidase inhibitors [1], using 1,2- and 1,3-diamine derivatives of dihydroxypyrrolidines as leads in the search for better inhibitors. Now, we present the synthesis of new bicyclic 1,2-diamines, as potential leads in the search for new active compounds, and their evaluation as glycosidase inhibitors. These bicyclic diamines can be seen as new non-peptide molecular scaffolds for the design of peptide analogues.



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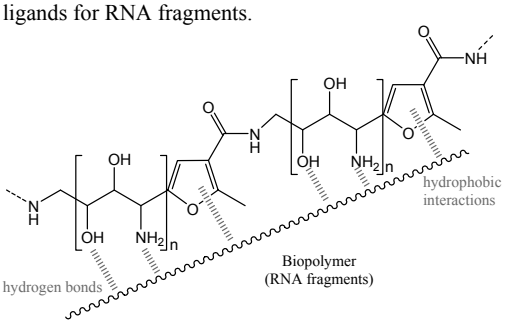
Action D34 **45**

Synthesis of Hetarylene-Peptidomimetics. An Approach to Heterocyclic-Aminopolyol Scaffolds for RNA Binding

A. J. Moreno-Vargas, A. T. Carmona, L. Molina, A. Ferrali, B. Picot, I. Robina

Dept. Organic Chemistry, Faculty of Chemistry, University of Seville, P.O. Box 553, E-41071 Seville, Spain.

RNAs provide potential targets to treat both infectious and chronic diseases [1]. In this communication we present the synthesis of new hetarylene-aminopolyols derived from polyhydroxyalkyl-furans as potential affinity ligands for RNA fragments.



The structure of our targets [2] is promising since several types of interactions could be expected with the biopolymer. The specificity for the biopolymer/ligand recognition will be controlled by the nature and sequence of groups and the chirality in the ligand.

[1] J. Gallego, G. Varani, *Acc. Chem. Res*. **2001**, *34*, 836.
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46

***N*-Acetyl-*L*-cysteine Protected Gold Clusters: Preparation, Characterization and Chiroptical Properties**

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Université de Neuchâtel, Institut de Chimie, Av. de Bellevaux 51, 2007 Neuchâtel, Switzerland

Gold clusters protected with *N*-acetyl-*L*-cysteine were prepared and characterized by transmission electron microscopy (TEM), UV-vis, NMR, CD and vibrational spectroscopy, in particular vibrational circular dichroism (VCD). TEM revealed very small particles with a maximum of the core size distribution below 2 nm. No significant surface plasmon resonance was observed in the UV-vis spectra, which confirmed the results obtained by TEM. ^{1}H NMR spectra showed that the *N*-acetyl-*L*-cysteine was attached to the gold clusters. The latter revealed pronounced VCD activity, especially in the asymmetric carboxylate and the amide I bands. Density functional theory (DFT) was used to simulate VCD spectra of N-acetyl-L-cysteine adsorbed on small gold clusters. The calculations revealed a strong dependence of the VCD spectrum on the conformation of the molecule. In contrast, the structure of the underlying metal particle seemed less important. Despite the several approximations inherent in such an approach, the calculated VCD spectrum of the most stable conformer was in good agreement with the measured spectrum, which indicates that VCD spectroscopy is a powerful tool for structure determination of molecules adsorbed on metal particles.
The particles could be separated according to size and charge by gel electrophoresis. Such separations revealed high abundance of certain particle sizes (magic numbers). The separated fractions showed distinctly different UV-vis spectra, exhibited different color and showed electronic circular dichroism activity in transitions located in the metal core. Possible origins of this optical activity are discussed.

47

Radical azidation of *B*-Alkylcatecholborane

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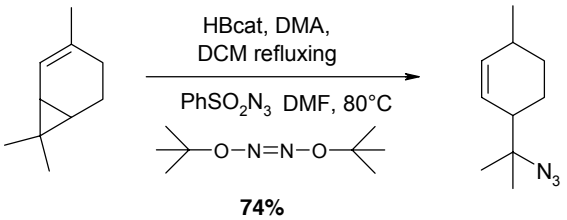
University of Bern, Freiestrasse 3, CH-3012 Bern, Switzerland

B-Alkylcatecholborane, easily prepared from hydroboration of alkenes, are excellent radical precursors [1]. We describe here a new methodology for their azidation based on the reaction of alkyl radicals with phenyl sulfonyl azide.



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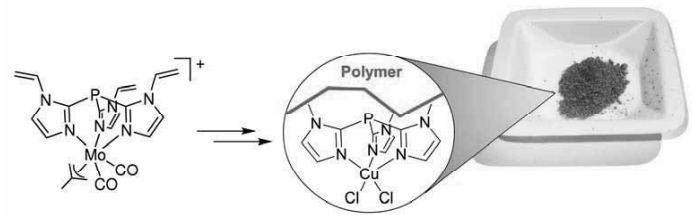
48

Highly Cross-Linked Polymers Containing N,N',N''-Chelate Ligands for the Cu(II) Mediated Hydrolysis of Phosphoesters

Alexander Schiller, Rosario Scopelliti, Kay Severin*

Institut des Sciences et Ingénierie Chimiques, Ecole Polytechnique Fédérale de Lausanne, BCH, 1015 Lausanne, Suisse

Copper(II) complexes of bi- and tridentate N-donor ligands such as bipyridine, terpyridine, and 1,4,7-triazacyclononane and their derivatives have been investigated intensively as artificial phosphoesterases. A general problem of these biomimetic hydrolases was found to be product inhibition and the formation of catalytically inactive hydroxy-bridged dimers. The immobilization of Cu-complexes on solid supports offers a potential alternative to reduce problems of aggregation.



Immobilized Cu(II) complexes were generated by a) homo polymerization of the N,N',N''-chelate ligand tris[2-(1-vinylimidazolyl)]phosphine (**1**) and subsequent metalation with $CuCl_2$; b) by co-polymerization of **1** with EGDMA und metalation with $CuCl_2$ or c) by molecular imprinting with an organometallic Mo-complex of **1** and EGDMA und replacement of Mo(II) by Cu(II). The ability of the polymeric Cu complexes to promote the hydrolysis of phosphoesters was investigated using the model substrates BNPP and NPP [1].

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49

Enantioselective oxidation with artificial metalloenzymes

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Oxidation reactions are among the most important transformations in synthetic chemistry. In recent years, several discoveries have revealed the potential of manganese catalysts for selective oxidations.

Inspired by the work of the groups of Eric N. Jacobsen and T. Katsuki we have developed biotinylated manganese(salen) complexes for enantioselective oxidation.

Based on the incorporation of achiral biotinylated organometallic complexes within (strept)avidin, artificial metalloenzymes are obtained, with properties reminiscent both of enzymes and of homogeneous catalysts[1]. Having established the proof-of-principle with hydrogenation and transfer hydrogenation reactions, we have recently focused on more challenging oxidation reactions.[1]

The results of aqueous epoxidation of alkenes and aqueous oxidation of sulfides with these artificial metalloenzymes will be presented.

[1] C. M. Thomas, C. Letondor, T. R. Ward, *J. Organomet. Chem.* **2005**, *in press*.