Selective Neuronal Nitric Oxide Synthase Inhibitors for the Prevention and Treatment of Neurodegenerative Diseases

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Nitric oxide (NO) is a ubiquitous biological messenger involved in a variety of physiological processes that acts as a signal transducer but also exerts a variety of regulatory and cytostatic functions. Nitric oxide synthase (NOS) is a family of homodimeric enzymes that catalyzes the oxidation of *L*-arginine to *L*-citrulline and nitric oxide in a NADPH- and O_2-dependent process. The constitutive endothelial isozyme (eNOS) is involved in the regulation of smooth muscle relaxation and blood pressure and in the inhibition of platelet aggregation. A second constitutive isozyme is neuronal NOS (nNOS), which is important for neurotransmission. A third isozyme is the inducible NOS (iNOS), which is located in activated macrophage cells and acts as a cytotoxic agent in normal immune responses.

The use of NOS inhibitors in pathologically elevated synthesis of NO has great therapeutic potential. NO overproduction by nNOS has been associated with neurodegeneration during stroke, spinal transmission of pain, migraine headaches, Parkinson's disease, Alzheimer's disease, Huntington's disease, and cerebral palsy. Compounds that inhibit nNOS would decrease the production of NO in the brain. However, because of the importance of NO to physiological functioning, potent as well as nNOS-selective inhibitors are essential.

This lecture describes the design of the first class of potent and highly dual-selective nNOS inhibitors and their modification for enhanced potency, selectivity, and lipophilicity. After the first selective inhibitors were obtained, X-ray crystallography and computer modeling guided additional modifications, and *de novo* structure-based design led to a new class of potent and selective nNOS inhibitors. Results of animal testing of some of these compounds for cerebral palsy will be described.

Medicinal Chemistry of Small Azaheterocycles: Design, Synthesis and Uses in Experimental Models of Hypertension, Diabetes, and Parasitic Diseases.

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Small azaheterocycles, such as benzimidazole, (benzo)thiazole, thiazolidine-2,4-dione, and 5-nitrothiazole belong a special group of molecules called "privileged structures". Privileged structures are usually rigid, heterocycle based structures defined as "a single molecular framework able to provide ligands for diverse receptors and also for multiple bioactivities".

Benzimidazole core has been associated with antiparasitic activity, and recently with vasoactive effect. Pimobendan, a benzimidazole derivative drug is effective in both acute and chronic heart failure and it also causes peripheral vasodilation. We synthesized a series of 1*H*-benzimidazole analogues of Pimobendan, substituted at position 5 with either $-CF_3$ or $-NO_2$, using a short synthetic route. 2-Methoxy-4-[5-nitro-1H-benzo[d]imidazol-2-yl]phenol was the most potent derivative of the series, showing an EC_{50} value of 1.81 μM and Emax of 91.7% for *ex vivo* relaxant response in intact aortic rings, resulting in a 2.5-fold higher activity compared to Pimobendan. The closely related 5-CF_3 analogue was 19 times less potent. The antihypertensive activity was evaluated at doses of 25, 50 and 100 mg/Kg, using spontaneously hypertensive rats (SHR), showing a statistically significant dose-dependent effect.[1]

Benzothiazoles has been related as ligand for multiple receptors and enzymes. We design and prepared a series of 2-arylsulfonylaminobenzothiazole derivatives focus on their antidiabetic activity. The *in vitro* inhibitory effect of the compounds against protein tyrosine phosphatase 1B (PTP-1B) and 11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1) was evaluated. Several compounds were rapid reversible (mixed-type) inhibitors of PTP-1B with IC_{50} values in the low micromolar range as well as active against 11β HSD1. The most active compounds were docked into the crystal structures of both enzymes. Docking results indicate potential hydrogen bond interactions between the ligands and the catalytic amino acid residues of enzymes. The most active in vitro compounds were evaluated for their in vivo antihyperglycemic activity in a type 2 diabetes mellitus rat model, showing significant lowering of plasma glucose concentration, during the 7 h post-intragastric administration.[2, 3]

Thiazolidine-2,4-diones (TZD) has been utilized as hypoglycemic agents. Fibrates, such as clofibrate has been employed as antidyslipidemic drugs. Our research group focuses on the modest structures of TZD and fibrates, and we designed and synthesized two hybrids of both pharmacophores. The spectrum of biological activity was calculated using the software PASS, which compute a prediction of the biological activity based on structural parameters. A molecular modeling and docking with PPARa and PPARy receptors were performed; validating the medicinal chemistry criteria taken in account for the compound design.[4]
Some other examples of antiparasitic benzimidazole and thiazole heterocycles will be presented in the lecture.

The *in silico*, *in vitro* and *in vivo* evaluations of the designed and synthesized azaheterocycles revealed that these compounds are interesting candidates for further research in the experimental therapeutics of hypertension, diabetes, dyslipidemias and parasitic diseases.

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Rational Drug Design for the Treatment of Castration Resistant Prostate Cancer

Michael E. Jung

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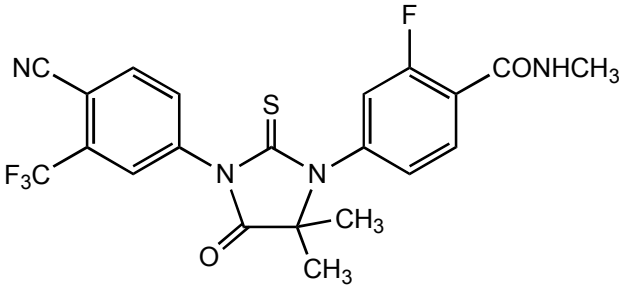
The chemistry and biology leading to the development of a super antagonist of the androgen receptor, MDV3100, for the treatment of castration-resistant prostate cancer will be described in detail. The structure-activity relationship study that led to its discovery will be outlined. The best hypothesis for why it actually kills the tumors will be presented. as will both preclinical and clinical data. Finally preliminary results on a newer antagonist, ARN509, will also be presented.



MDV3100

Public-Private Partnerships: The New Face of Innovation in Drug Discovery. New Approaches to Treat Amyotrophic Lateral Sclerosis

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The discovery of new drugs to treat unmet medical need is a worthy and important human endeavor. New advances in our understanding of the molecular basis of disease have resulted in innovative small-molecule therapeutics that has revolutionized patient care for many indications. However, there has been an unexpected decrease in the productivity of biomedical research in the past decade, in which 30-50% fewer new molecular entities (NMEs) are being approved each year when compared to the rate of NME introduction in the 1990s. In 2010, only 22 NMEs were approved by the U.S. FDA even though spending on drug discovery research is now many times higher than in previous decades and important new enabling technologies have been developed and validated. This pipeline problem is associated with the difficulties of translating basic biochemical discoveries into preclinical development compounds suitable for entry into human clinical trials. These challenges are particularly severe for the infectious, neglected diseases that afflict one-sixth of humanity. An unexpected disconnect has developed, called the "valley of death", between the translation of exciting new discoveries about the molecular basis of disease into preclinical development compounds suitable for acceptance into the costly and risky preclinical and clinical development programs required for human clinical use. More drugs are being approved today from small companies than large ones, as major pharmaceutical companies are removing high-risk research efforts off of their portfolio. The Pennsylvania Drug Discovery Institute (PDDI) was created to promote technology transfer and innovation in a biotechnology accelerator facility environment. ALS Biopharma, LLC is an emerging biotechnology company affiliated with the PDDI that was established to provide therapeutic relief for the debilitating condition of amyotrophic lateral sclerosis (ALS). ALS is the most prevalent motor disorder, afflicting 40,000 Americans and 200,000 individuals worldwide. The disease imparts tremendous suffering upon patients and caregivers alike. New developments in the biochemistry and genetics of the disease provide new hope that targeting approaches in early drug discovery will afford disease modifying therapies. This talk will discuss our efforts focused on target validation and hit to lead medicinal chemistry for the treatment of this debilitating disease. We are taking both biologic protein-based and small-molecule approaches to treat ALS, investigating modulation of the heat shock response and the nucleic acid binding protein TDP-43.

Stereodivergent Synthesis of Aminophosphonic Acids and Derivatives

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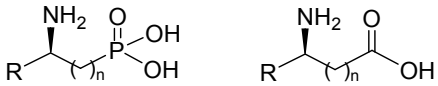
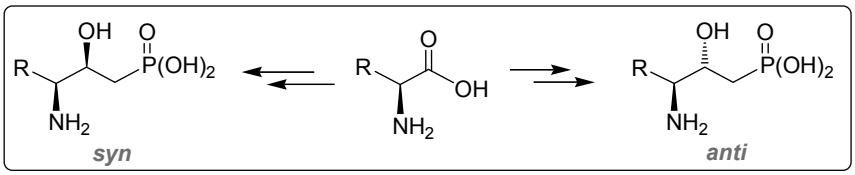
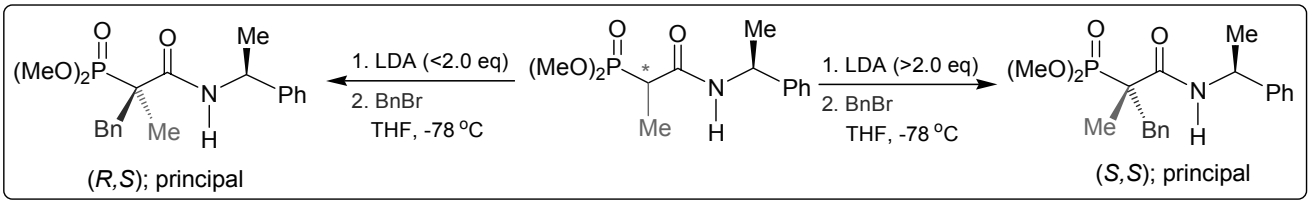
Aminophosphonic acids are mimetics of amino acids. In this class of compounds, the planar and less bulky carboxylic acid (CO_2H) is replaced by a tetrahedral phosphonic acid functionality ($P(O)(OH)_2$). This difference between these two types of compounds is reflected in their shape, acidity, and several other properties. Aminophosphonic acids and their derivatives have interesting biological and biochemical properties,[1] and in the last years there has been a tremendous leap in the development of suitable synthetic methodologies for their preparation.[2]

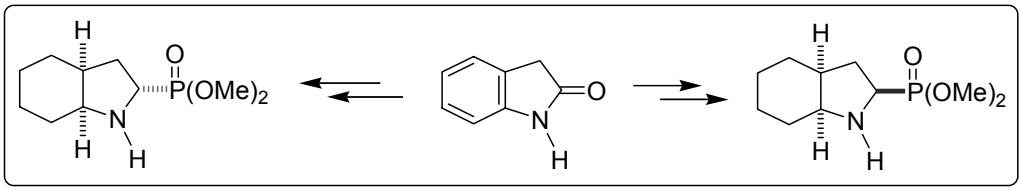


n = 0, 1, 2

Taking into account the biological properties associated with the aminophosphonic acids and derivatives, and in continuation of our effort on the development of new synthetic methods for the stereoselective synthesis of new aminophoshonates,[3] the lecture will involve the stereodivergent synthesis of γ-amino-β-hydroxyphosphonates, quaternary α-aminophosphonates and new conformationally restricted α-aminophosphonates.







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The β- and γ-Peptides Built of Homologated Proteinogenic Amino Acids from Synthesis to Structure to Microbiological to Biomedical Investigations.... and Back

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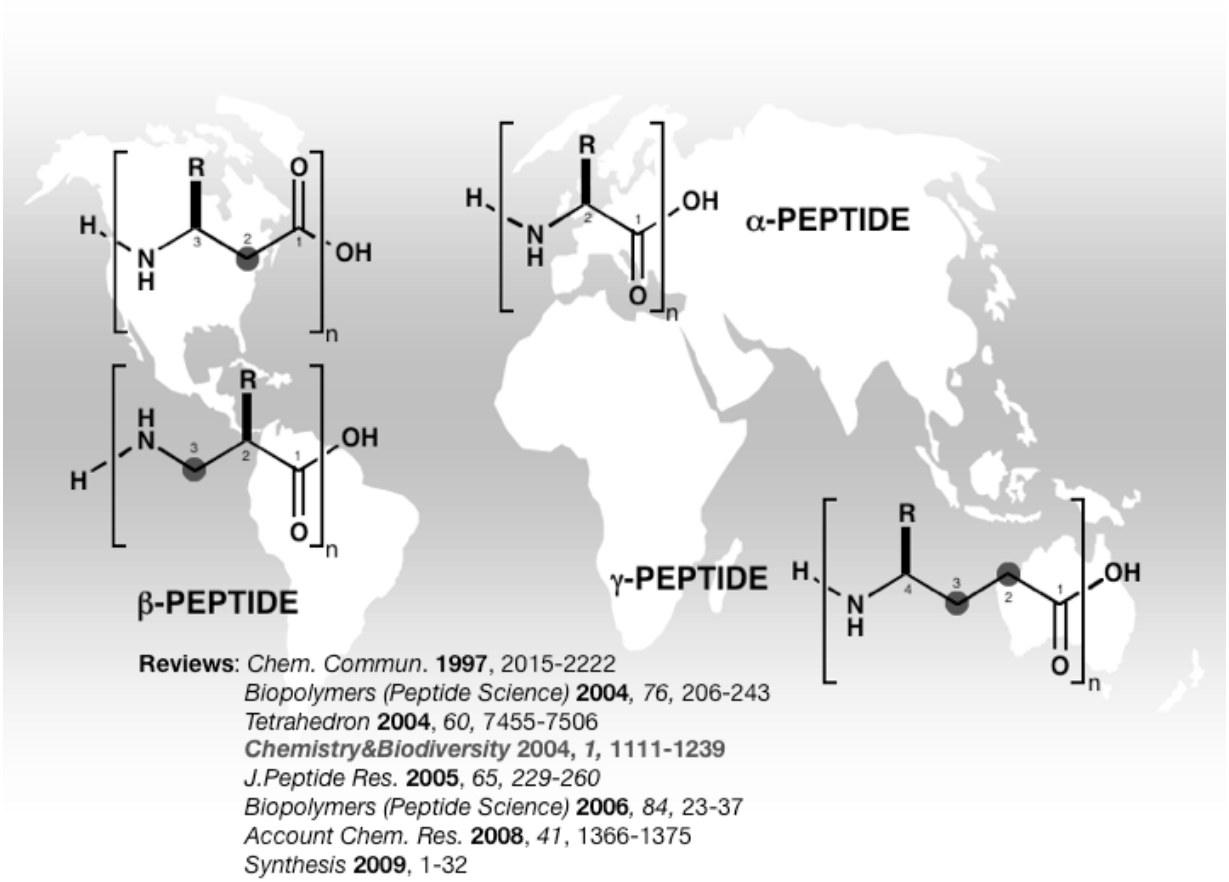
The insertion of a simple CH_2-group into each and every residue of a peptide with proteinogenic side chains opens a door into a new world with similarities and, at the same time, fundamental differences of structures. The journey into this world was only possible by hard-core organic syntheses. The biological tests of proteolytically, as well as metabolically stable β-peptidic mimics of a number of α-peptidic natural products will be described. The biological investigations have led to the discovery of β-peptide-cleaving enzymes which can be used for kinetic resolutions of β-amino acids.



Scorpion Peptides: Structure and Function

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Our laboratory studies the venom components from scorpions, because Mexico is the richest country on biodiversity of these arachnids and human accidents in the country are in excess of a quarter of million people per year; being a real public health problem. From 221 different species in Mexico, out of approximately 1600 in the world, there are seven which contain toxic peptides to mammalians, all belonging to the family *Buthidae*, genus *Centruroides*. We dedicated a substantial part of more than 35 years to the isolation and chemical characterization of proteins and peptides from scorpions. Most sequencing was done by Edman degradation of pure peptides, but also information on the primary structure of these toxins came from cloning genes of the venomous glands. Additionally, the three dimensional structure of several classes of peptides were obtained by nuclear magnetic resonance studies and the pharmacological action was assessed by electrophysiological measurements using excitable and none excitable cells by the use of patch-clamping systems. At this moment over 400 such peptides are known (Possani and Rodríguez de la Vega, in "Handbook of Biologically Active Peptides" (Ed. A.J.Kastin) Academic Press, San Diego CA, USA, 2006). Medically important peptides to humans are those peptides that contain from 59 to 73 amino acid residues, cross-linked by 4 disulfide bridges, showing high affinity (nanomolar range) towards ion-channels that control Na^+ permeability through biological membranes. These toxins usually modulate the opening (alpha-toxins) or closing mechanisms (beta-toxins) of Na^+-channels (Possani et al., Eur. J. Biochem. 264:287, 1999). In addition another important family of peptides is responsible for blocking K^+-channels. The first K^+-channel blocker described in the literature and named Noxiustoxin, from the scorpion *C. noxius* (Carbone et al. *Nature* **1982**, *296*, 90) as well as Ergtoxin-1 (Gurrola et al. FASEB J. 13:953, 1999), the first peptide that block K^+-channels of the ERG family (*ether-a-go-go* family of genes) responsible for heart arrhythmias were described by our group. For many years chemical synthesis of fragments of these peptides was prepared, aiming at the development of a vaccine against scorpion envenomation. Scorpine (Conde et al. *FEBS Lett.* **2000**, *471,*165) and Hadrurin (Torres-Larrios et al., *Eur. J. Biochem*. **2000**, *267*, 5023,), two peptides with antibiotic and anti-parasitic activities, and heterodimeric phospholipases (Zamudio et al. *J. Biol. Chem*. **1997**, *272*, 11886) were also found. Immunodulatory peptides such as Vm23 and Vm24 that recognize Kv1.3 sub-types of K^+-channels in human lymphocytes were protected by patent (WO 2008/139243). Presently, we are conducting experiments related to the proteomic analysis of these components and transcriptome analysis of genes present in the venomous glands. We are looking at the genomic organization of the genes that code for scorpion components, we are investigating the secondary molecular events that take place after scorpion stings, we are expressing heterologously these peptides for improvement of available anti-venoms, as well developing human fragments of neutralizing antibodies (scFV), (see Riaño-Umbarila et al*. FEBS J.* **2005**, *272*, 2591). A three-dimensional structure of a toxin-scFV complex was recently obtained by X-ray diffraction (Canul-Tec et al., *J. Biol. Chem*., submitted **2011**). Several examples illustrating these findings will be presented during the meeting.

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Design of Novel Peptide and Peptidomimetic Ligands for Disease States that are Stable and Bioavailable

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It has been difficult to develop effective drugs for degenerative diseases such as cancer, prolonged and neuropathic pain, diabetes, cardiovascular disease, etc. A hallmark of all of these diseases is that they develop from changes in the expressed genome. Consideration of these changes can lead to new approaches for drug design and development involving considerations of multivalency with multiple receptors/acceptors. This design paradigm requires careful structural and conformational considerations of how the different pharacophores should be combined and synthesized to enhance potency and efficacy for all of the targets. When done properly, considerable synergy in biological potency and efficacy can be obtained. We will discuss this approach for the design of multivalent ligands for the treatment of prolonged and neuropathic pain, for which there is no current effective therapy, and for the detection and eventual treatment of cancer. Consideration of changes in the expressed genome are critical for the design of drugs for the disease state. The design, synthesis and biological activities of these novel multivalent ligands will be discussed.

Support by grants from the U.S. Public Health Service, National Institutes of Health (NIH)

New Methodology for the Synthesis of Peptides, Glycosides, and their Conjugates

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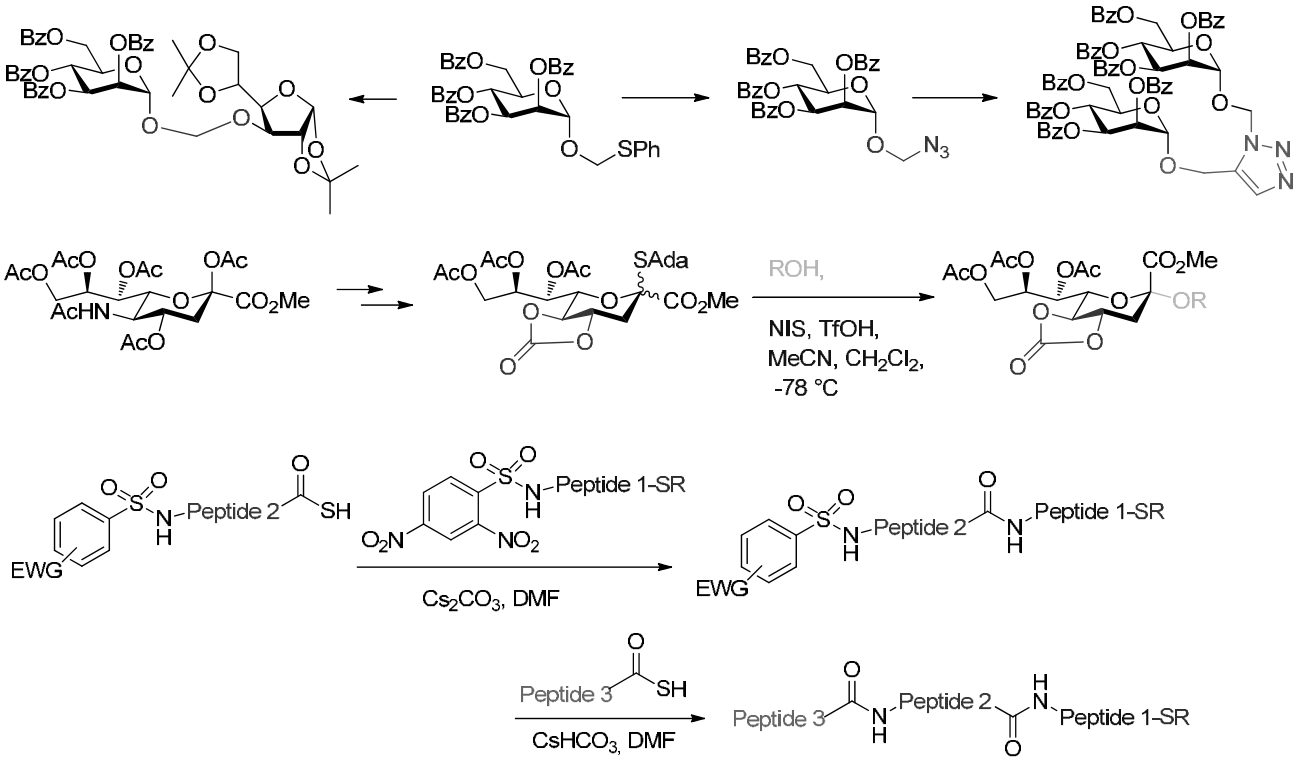
Research in the Crich group targets the mechanism-based development of new methodology for the solution of contemporary problems in organic synthesis. Current themes include the stereocontrolled synthesis of the more challenging types of glycosidic bond such as the α-sialosides,[1] methodology for the block synthesis of peptides,[2] and the development of new ligation reactions.[3,4] Aspects of these and other ongoing projects will be presented.



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Synthesis and Enzymatic Resolution of Beta-Amino Acids

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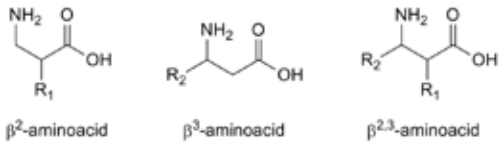
β-Amino acids have unique pharmacological properties and their utility as building blocks of β-peptides, pharmaceutically important compounds and natural products is of growing interest.[1] This arises, for instance, from the ability of β-peptides to fold to secondary structures in predictable ways. Several review articles on the asymmetric synthesis of β-amino acids are available.[2] This work cover the enzymatic methodology developed for the preparation of various highly enantiopure β^2- β^3- and $\beta^{2,3}$-amino acids (Scheme 1) in kinetic resolutions of racemic mixtures.[3]

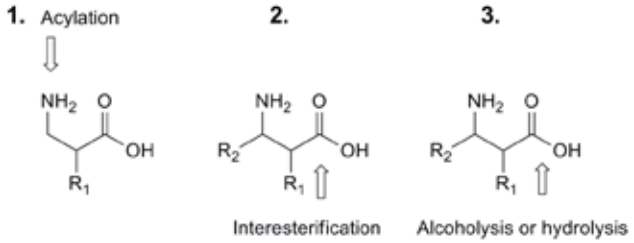


Scheme 1. General structures of β-amino acids.

A plethora of methods have been used for the preparation of racemic β-amino acids. For example, β-amino acids have been prepared by hydrolysis of β-amino nitriles, homologation of α-amino acids, Michael type additions to double bonds, Knoevenagel type condensations of an aldehyde and malonic acid in the presence of ammonium acetate, amidomethylation of aryl acetic or malonic esters, oxidation of amino alcohols, ring opening of β-lactams, transformation of a carboxylic functionality of a dicarboxylic acid into an amine, reductive amination, and reduction of α-cyano carboxylic esters.

The main chemo-enzymatic paths for obtaining highly enantiopure β-amino acids are based on the kinetic resolution of racemic β-amino acids or some of their derivatives. The resolutions of β^2-amino acids have not yet been studied to the same extent as their β^3- and $\beta^{2,3}$-counterparts.

The most successful approaches to the enantiomers of β-amino acid derivatives by CAL-B are shown in Scheme 2 in general forms. The first method is based on highly chemoselective *N*-acylation. In the second method, the reaction is directed to the ester group, and in the third method an *N*-protected β-amino ester.



Scheme 2. Strategies for the kinetic resolution of β-amino acid derivatives.

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New Highlights in Peptide Synthesis

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Our Institute is involved in the synthesis of biomolecules and the study of their *in vitro* pharmacology. Among these biomolecules, amino acids, peptides and proteins represent a well studied family. In this presentation, several new methodologies that have been developed in our Institute during the last few years will be discussed.

They mainly concern:

- The use of O-N acyl migration that has been recently proposed in several laboratories for the synthesis of difficult peptide sequences, including β-amyloid peptide fragments (*Sohma et al., Chem. Commun., 2004; Mutter et al., Angew. Chem. Int. Ed., 2004; Carpino et al., Tet. Letters, 2004; Sohma & Kiso, ChemBioChem, 2006*) for the synthesis of (i) cyclic peptides (*Lecaillon et al., Tetrahedron Lett., 2008*) of different sizes; (ii) peptide alcohols, including peptide antibiotics and sandostatin (*Tailhades et al., Angew. Chem. Int. Ed., 2010*); (iii) peptide oligomers, with the development of an original polymerization strategy (*Tailhades et al., unpublished results*).

- The development of new chemistry involving amino acid derivatives such as N-carboxyanhydrides (NCA) and diketopiperazines (DKP) for the synthesis of (i) peptides in « solid » media, without solvent (*Declerck et al., Angew. Chem. Int. Ed., 2009*); (ii) supported reagents for the formation of disulfide bonds in peptides (*Cristau et al., PCT Int. Appl., WO 2007144411, Verdie et al., unpublished results*); (iii) of chiral pyrrolidine-2,4-diones through the Transannular Rearrangement of Activated Lactams (TRAL reaction) (*Farran et al., Angew. Chem. Int. Ed. 2007; Org. Letters, 2007; Org. Biomol. Chem., 2008; Eur. J. Org. Chem., in press).*

- The development of new reactants as « signal enhancers » in mass spectrometry and some of their applications (*Paramelle et al., Proteomics, 2009; Angew. Chem. Int. Ed., 2010*).

New Activation Modes and Concepts in Organocatalysis

Karl Anker Jørgensen

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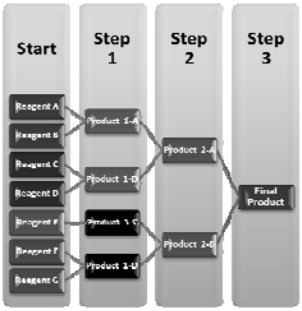
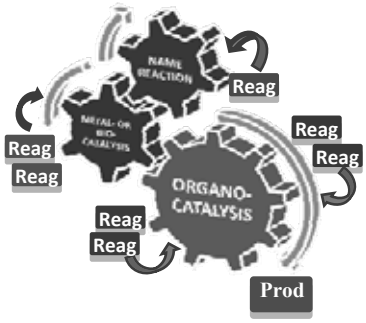
The lecture will outline a new activation mode in organocatalysis and discuss the activation mode in relation to the traditional activation concepts. Furthermore, the combination of these activation concepts will be applied as a strategy for the one-pot construction of highly functionalized optically active molecules.





Ball Milling as "Green" Tool in Asymmetric Organocatalysis

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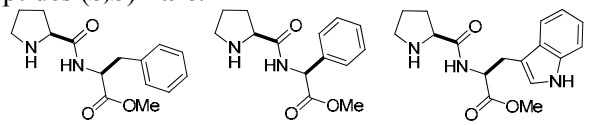
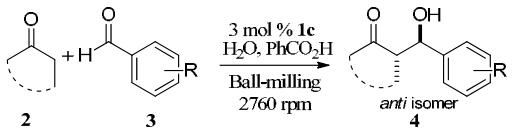
Mechanochemistry deals with the mechanical cleavage of intramolecular bonds by external force. The way to provide such mechanical impact can arise from grinding, milling, shearing, scratching, polishing or rapid friction. In particular, High-speed ball-milling (HSBM) is a sustainable mechanochemical technique, which has commonly been used for milling minerals into fine particles. In the area of synthetic organic chemistry, this technique has been successfully used to promote several solvent-free reactions. However, until now the use of ball milling in organocatalysis has been limited. As a part of our interest to contribute in the area of chemical development in a sustainable manner, we prepared a series of (*S*)-proline-based dipeptides **1a-c** (Figure) and evaluated them as organocatalyst in asymmetric aldol reaction under solvent-free conditions using the HSBM technique.

Figure. Structure of dipeptides (*S,S*)-**1a-c**.



Following an thorough examination of the essential parameters, e.g. catalyst, amount of catalyst, presence/absence of water and additives, it was found that dipeptide (*S,S*)-**1c** is the most efficient catalyst. The application of (*S,S*)-**1c**, as organocatalyst in the direct asymmetric aldol reaction between cyclohexanone **2a** and cyclopentanone **2b** with several benzaldehyde derivatives containing different acceptor and donor substituents (**3a-d**) is summarized in the Table.

Table. Direct asymmetric aldol reaction catalyzed by dipeptide **1c** under ball-milling conditions.[a]



2 **3** **4**

Entry	R	Yield [%][b]	*dr* (*anti/syn*)[c]	*ee*[%][d]
1	4-NO_2	89	92:8	>98
2	2-NO_2	86	98:2	94
3	2-Cl	77	94:6	90
4	2-CF_3	62	96:4	90
5[e]	4-NO_2	73	40:60	80

[a] Kketone **2a-b** (0.22 mmol), aldehyde **3a-d** (0.20 mmol), Cat. **1c** (3 mol%), -20ºC, 1.1 equiv H_2O, $PhCO_2H$ (5 mol%), 6.0 h. [b] Isolated yield. [c] Determined by ^1H NMR of the crude product. [d] Determined by chiral HPLC. [e] Cyclopentanone was used.

The results show that the reaction proceeds efficiently affording the *anti* aldol product with good diastereo- and enantioselectivities. The excellent diastereoselectivity observed in the aldol products using catalyst (*S,S*)-**1c** in contrast with (*S,S*)-**1a** and (*S,S*)-**1b** is explained in terms of π-π interactions between the aromatic substrate and the tryptophan rings.

Lewis Base Activation of Lewis Acids: A New Paradigm for Catalysis in Main Group Chemistry

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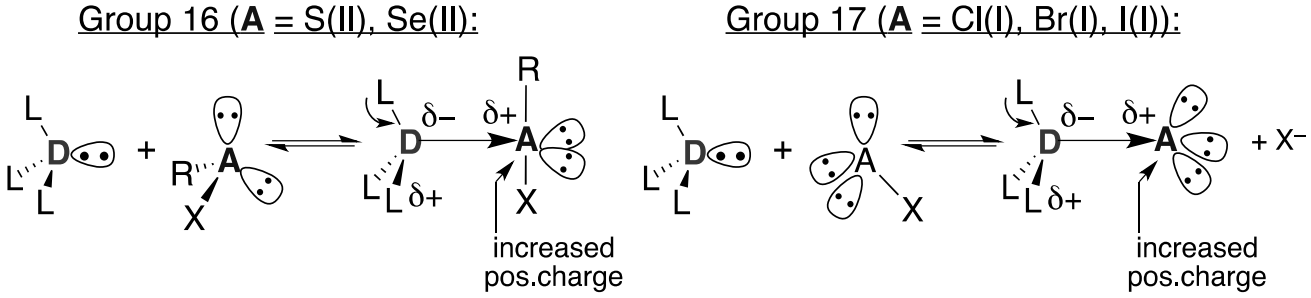
Catalysis is a chemical evergreen. Ever since Michael Faraday first recognized that platinum wire could bring about the combination of hydrogen and oxygen with spectacular speed, chemists have been fascinated with the origins, principles, scope and applications of catalysis. Despite Berzelius's unfortunate choice of the word for this phenomenon (from the ancient Greek for destruction), the field of chemical (abiological) catalysis has grown immensely in the past century. Surprisingly, however, catalysis of reactions of the p-block (main group) elements is almost non-existent. Over the past decade, we have investigated reactions based on elements in Groups 14, 16 and 17, under the newly developed paradigm of "Lewis-base activation of Lewis acids". This lecture will describe the most recent efforts in our laboratories to design, understand and apply synthetically useful cyclofunctionalization reactions of the halogens and the chalcogens under catalysis by Lewis bases.



Bonding Boron to Aromatic Metalation Synthetic Strategies

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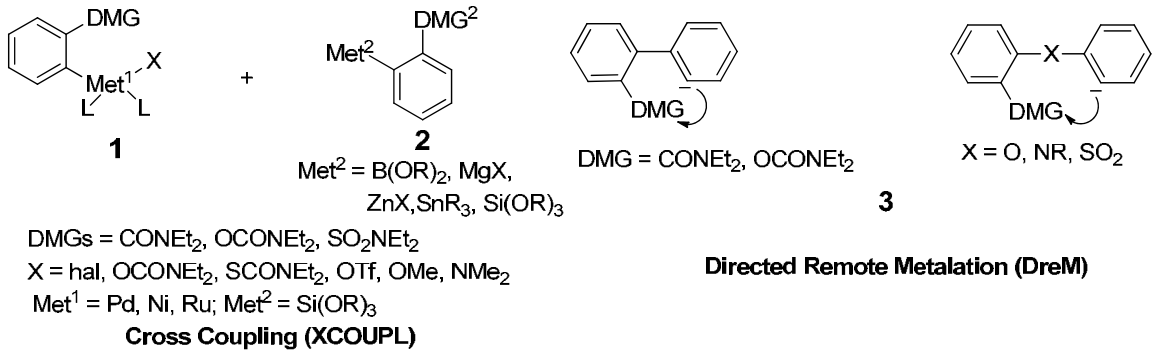
Synthetic organoboron chemistry, originating with the work of H.C. Brown and his students, was catalytically activated, in the late 1970s, by the discoveries of A. Suzuki which we honor today but have celebrated from October, 2010 in a much broader context. Our group has established a simple links between the Directed *ortho* Metalation (DoM) reaction and the rich transition metal catalyzed cross coupling chemistry (**1** + **2**) of Mg, Zn, and especially B, and the enabling Directed remote Metalation reactions (**3**). In the interim, we have discovered the *latency* of directed metalation groups themselves ($OCONEt_2$, $SCONEt_2$, SO_2NEt_2) in cross coupling reactions. Using these connections had led to the development of new regiospecific strategies for the construction of aromatics and heteroaromatics. Recent results from our laboratories will be described.



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Use of Organometallic Compounds in the Activation and Transformation of Molecules of Interest in the Industry

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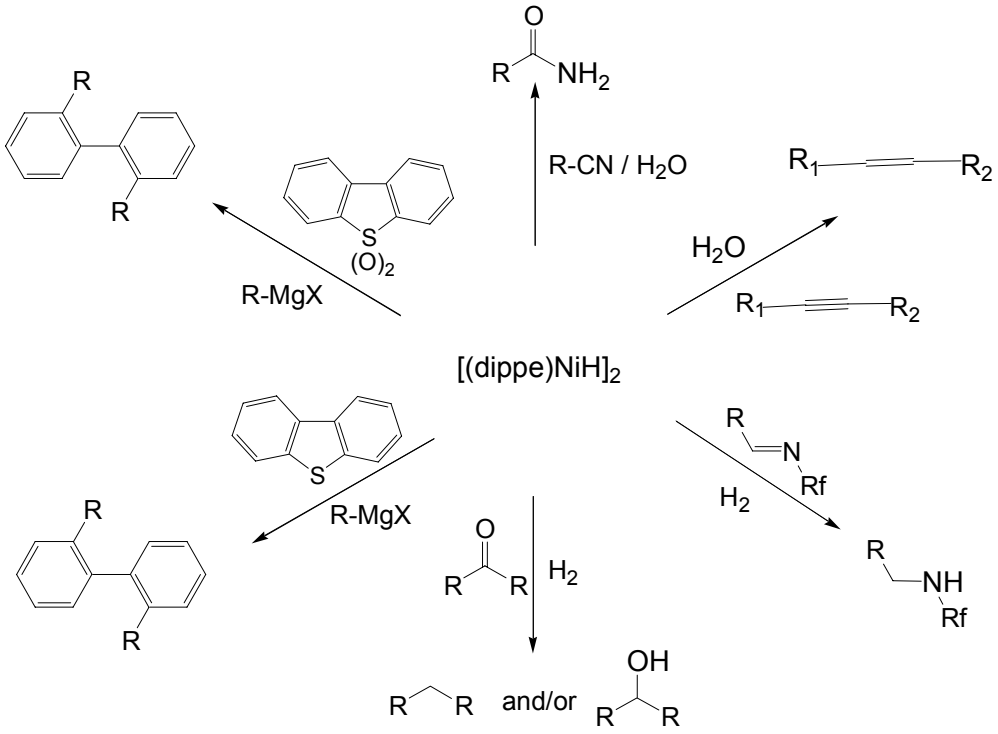
One of the most important challenges in modern chemistry is the achievement of environmentally friendly synthetic methods, with low or none impact in Mother Nature. However, many of the raw materials available or the pollutants generated in a variety of process usually display high stability due to the presence of strong and unreactive bonds such as C-C, C-H, C-S, C-N, C-F, C-Cl and C-O bonds. The activation of these bonds can be achieved with the use of a metal center, along with the right ancillary ligands to produce a metal mediated or a catalytic process.

Our group has made few contributions in the field of activation of strong bonds and implemented methodologies for the preparation of a wide variety of organic compounds, relevant for both industry and academia (see scheme). Some of these will be discussed in detail during the presentation.



Organotrifluoroborates: Novel Reagents and Reactivity

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Hirschmann-Makineni Professor of Chemistry
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Innumerable improvements on the original Suzuki coupling reaction have been recorded, including vastly improved catalyst/ligand systems, unique solvents, and enhanced experimental conditions. Until recently little effort has been expended toward further development of the most important component of the process – the organoboron reagent itself.

Boronic acids, commonly used for Suzuki-Miyaura coupling, are far from ideal. Many of these reagents are difficult to purify because they are waxy solids. Because of competitive protodeboronation, literature protocols for cross-coupling employ excess boronic acid to insure a complete conversion of the electrophilic component of the reaction.

Most importantly, all trivalent organoboron species are susceptible to reactions with important classes of reagents commonly utilized in organic synthesis. Consequently, these organoborons are normally either purchased or prepared and then utilized directly in the Suzuki cross-coupling reaction, limiting synthetic approaches to target molecules of interest.

The more robust organotrifluoroborate reagents to be discussed provide a solution to these problems, expanding the range of retrosynthetic pathways using Suzuki coupling reactions as key transformations for synthesis of valuable organic materials. New reagents and novel transformations will be discussed.

Molecular Design of Acid Catalyst for Asymmetric Synthesis

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New reagents and catalysts have unlimited potential for the future of organic synthesis. We have been interested in Lewis and Brønsted acid catalysis for a number of years. In this lecture, I am going to focus on several of these acid and related catalysts from the aspect of their molecular design and engineering.

Acid is the classical reagent in organic synthesis. Lewis and Brønsted acids can be utilized as more effective tools for chemical reactions by sophisticated engineering such as “designer acids”. Needless to say, the ultimate goal of such “designer acids” is to achieve high reactivity, selectivity, and versatility as a useful tool of organic synthesis. Even now, the full potential of acid catalysts has not yet been realized. One possible way to take advantage of such abilities may be to apply a “combined acids system” to the catalyst design. The second approach is the combination of super Brønsted acid and super silyl group to establish a cascade reaction to generate complex molecules in a single pot. The lecture will be focused on these two concepts for designing acid catalysis.

Tailor-Made Metal Catalysts for More Efficient, Sustainable Synthetic Protocols

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The advent or renaissance of several metals as catalysts for the formation of C_{aryl}-C, C_{aryl}-O, C_{aryl}-S and C_{aryl}-N bonds has revolutionized this fundamental area of synthetic chemistry in the last decades. Moreover, an increasing number of transformations, previously unexplored or with serious limitations due to the requirement of toxic transmetallating agents/stoichiometric amounts of catalysts, can now be conducted with the aid of palladium and copper catalysts. In addition to an improved catalytic efficiency (substantial reduction of the relatively high amounts of the catalysts required), much effort has been devoted to the development of more sustainable conditions, such as the recovery of the catalyst or the use of environmentally more friendly and safer reaction media.[1]

In this context, our research has been focused on two main areas, the synthesis and application as catalysts of suitably designed palladacycles, and the use of copper catalysts in reactions previously monopolized by precious metals like palladium, platinum and rhodium. For both cases, the aforementioned sustainability criteria have been incorporated to some extent in the synthesis of several carbo- and heterocyclic systems. Therefore, in addition to more convenient catalyst sources, the minimization of their loadings, their recycling and the use of safe, cheap and environmentally friendly reaction media will be also discussed.[2]

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Transition Metal Complexes with Two Families of Nitrogen Donor Ligands: Triazenido and Tri(pyridyl)imidazolines

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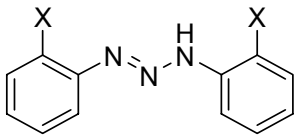
The use of compounds with nitrogen donor atoms as supporting ligands in the chemistry of transition metals has received considerable attention during the last decades. Our research group has focused its interest on new N-donor ligands and their transition metal complexes, which can be grouped in two families: triazenido and tri(pyridyl)imidazolines.

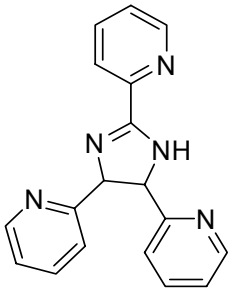
Triazenido ligands. With the aim of better controlling steric and electronic properties of the ligand to manipulate the reactivity and potential catalytic activity of their complexes, a series of *ortho* functionalized 1,3-(bis)-aryltriazenes are being prepared. This involves the design and development of bis(bidentate) and tridentate ligands in order to anchor two metal centers and keep them in close proximity. Complexes with metal ions such as Cu(II),[1] Cu(I),[2,3] Pd(II),[4] Pd(I),[4] Ag(I),[2] Rh(III),[5] Ir(III) have been prepared and their structures determined. Palladium complexes show catalytic activity in C-C coupling reactions.

Tri(pyridyl)imidazolines. Given the strong affinity of late transition metals for pyridine-based ligands, the coordination behavior of a series of 2,4,5-tri(pyridyl)imidazolines towards various metal ions is being explored. Complexes with metal ions such as Mn(II),[6] Ni(II),[7] Cu(II),[7] Zn(II),[7] Rh(I), Ag(I), Cd(II),[8] Ir(I), Hg(II)[9] have been prepared and their structures determined. Different coordination modes, which depend on the metal ion, counterion and solvent, are observed. In some of these complexes, interesting non-covalent interactions are observed, which may influence the coordination number and geometry. Also, the first coordination polymers with these ligands have been prepared.

LIGAND PRECURSORS



Triazenes



Tri(pyridyl)imidazolines

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Farnesylated Proteins. A Method for the Regioselective Immobilization of Proteins.

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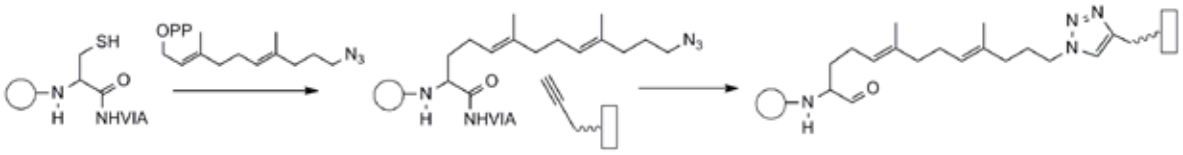
Microarrays based on protein chips are useful in a wide variety of applications that involve detecting and measuring protein-protein interactions, protein-small molecule interactions, and products of enzyme-catalyzed reactions. Immobilized proteins are adsorbed on surfaces through non-covalent interactions or are tethered covalently. Typically the immobilization protocols give surfaces coated with proteins in a heterogeneous collection of orientations and result in reduced binding interactions between the immobilized proteins and species in solution.

Eukaryotic proteins bearing a signature carboxy-terminal CaaX sequence, where C is cysteine, a is a small aliphatic amino acid, and X is Ala, Met, Ser, or Gln, are modified with farnesyl diphosphate to give a cysteinyl thioether. The reaction, catalyzed by protein farnesyltransferase (PFTase), is highly selective for the CaaX recognition motif. Of primary importance, PFTase will selectively add a farnesyl residue to virtually any peptide or protein that bears the Caax sequence. Because CaaX modifications are absent in bacteria, it is possible to selectively farnesylate a wide variety of soluble recombinant proteins bearing the carboxy-terminal modification.

We have synthesized alternate substrates for PFTase containing functional groups that allow us to attach the proteins to surfaces derivatized with complementary groups in a bioorthogonal reaction. Thus, the proteins are



attached to the surface regioselectively through the CaaX cysteine. The immobilized proteins retain their native folds and functions. This approach for immobilization offers a method for construction of microarrays with all of the attached proteins attached in the same orientation.

Materials for Energy Applications

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Energy shortage and environmental pollution are two major problems in this century. Current energy resources are basically based on carbon, oil, natural gas, hydro-power and nuclear reactions. Unfortunately their use has led to a massive emission of CO_2, NOx and other contaminants such as hydrocarbons and sulphides. Additionally, oil reserves are now very much reduced and its cost increases continuously. Naturally then development of clean and novel sources of energy has become very important. The most obvious alternative source of energy is the Sun although currently with a low efficiency of conversion. Thus research on more efficient solar cells is relevant. Photovoltaic lab solar cells based on Si reach around 24 % conversion efficiency with a high fabrication cost, commercial cells reach around 15 to 20 % efficiency. The limit for these cells is a conversion of 31 % from the total solar spectrum. Thus several methods have been proposed to increase efficiency and reduce fabrication costs. The third generation solar cells are produced with novel materials (organic and inorganic) and an effort is made to promote effects such as carrier multiplication with the use of nanostructured materials. Multiple exciton generation (MEG) is produced when electron-hole pairs originated by the incoming photon are confined by a nanoparticle or quantum dot. MEG can help increasing the conversion efficiency beyond 100 %.

The development of materials for such new devices depends upon synthesis lead by a convenient structural characterization and measurement of properties. New nanoestructured materials for photovoltaic application are required for the current designs of new solar devices. For example, there are currently several techniques to integrate nanoparticles or quantum dots to thin film solar cells: first, organic-inorganic hybrid devices containing dispersed nanoparticles in a polymeric matrix (acting as a semiconductor type p) and secondly, inorganic devices consisting of a double layer of semiconducting nanocrystals type p and n. These methods and the materials in use, and most likely to be successfully used, will be reviewed in this presentation with specific examples.

Nanostructures are definitely an interesting alternative for better photovoltaic materials that can lead to more efficient solar cells. The size is an important variable that can offer a myriad of possibilities and alternatives. Nevertheless characterization at such levels becomes very demanding. The required techniques must fulfill spatial and analytical resolutions at the atomic scale. Electron microscopy is one of them but it needs to be applied with the highest possible care to produce useful results. Characterization of photovoltaic materials by electron microscopy techniques will be also addressed in this presentation with specific examples regarding measurement of important variable (energy gap in semiconductors), determination of chemical composition and structure with the highest possible resolution at the atomic level.

Poly (Lactic Acid) Derivatives: Synthesis and Characterization of Nanofiber Scaffolds

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Poly(lactic acid), PLA, is a thermoplastic biodegradable material highly attractive for several medical and biological applications. These applications of PLA arise from its biocompatibility; it degrades as lactic acid which is metabolically innocuous. PLA can be obtained by several routes and it can be can be transformed easily into nanofibers, nanofilms and other products. The fibers can be fabricated in various forms for implants, sutures, drug delivery systems, and more recently as scaffolds for tissue engineering. This work focusses on the synthesis of PLA derivatives and the characterization of nanofibers and scaffolds fabricated by electrospinning.

The chemical routes used for the functionalization and grafting of PLA on other polymers such as PLA and 2-hydroxiethyl-methacrylate grafted on poly(phosphazene), PLA modified with maleic anhydride and grafted on collagen, and grafting of PLA on the surface of hydroxiapatite nanoparticles, will be first discussed. The characterization of the PLA derivatives as well as the morphologies of nanofibers and scaffolds, prepared by electrospinning in our laboratory, will be also presented and related to the processing parameters used to obtain these materials. Finally, the main effects of the chemical structure as well as nanofiber and scaffold dimensions, mechanical properties and morphologies in the field of tissue engineering will be introduced.

Electrocatalysts: from Synthesis and Characterization to Prototypes

Omar Solorza Feria

Departamento de Química. CINVESTAV-IPN

Electrocatalysts nanotechnology is an emerging area of interest, which opens up new possibilities of applications of novel materials demanded in the renewable energy sector and for many applications including transportation, distributed power and portable power systems. Most of the research in advanced electrocatalysis is performed on powders containing nanometric-sized particles. Because of the energy generators efficiency is related with the catalyst activity, *i.e.,* the size, geometry, composition, and dispersion of its particles, it is important to control these factors during the synthesis process.

The present communication is aimed to present our recent studies on the synthesis and characterization of electrocatalysts for fuel cells application in different low power prototypes such as is shown in pictures bellow.