SLB-PL1

Enantioselective Heck Reactions with Aryldiazonium Salts. Challenges and Synthetic Opportunities

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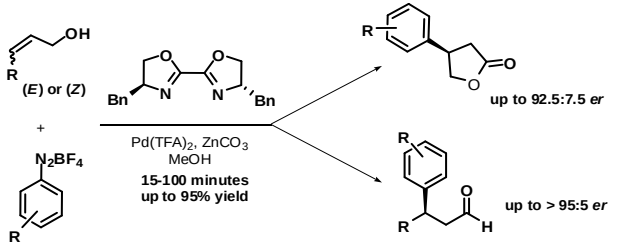
Enantioselective catalysis has revolutionized the field of organic synthesis and has brought significant scientific and economic benefits for our society. The enantioselective arylation of olefins in particular (Heck reaction) has been a subject of intense academic and industrial interest due to its potential for providing enantiomeric enriched medicines, fragrances and new materials, which are in general more selective and less toxic than the racemic counterpart. In this context, the Pd-catalyzed coupling of arenediazonium salts to olefins (Heck-Matsuda reaction) stands as a more practical and reliable method to access structurally complex organic molecules than the conventional Heck protocols. The Heck-Matsuda arylations can be easily performed in the lab under aerobic conditions without requiring expensive and/or toxic phosphine ligands. The first examples of these reactions were described by Tsutomu Matsuda in 1977. However, in spite of the many advantages and the long-term existence of this reaction, its enantioselective version has, until recently, constituted a considerable challenge due to the intrinsic incompatibility between the ordinary phosphine ligands and the arenediazonium salts. In this lecture, the first examples of effective enantioselective Heck-Matsuda reactions will be presented using chiral bisoxazoline ligands.[1] Some recent developments from our lab will also be highlighted.



Scheme: Intermolecular Enantioselective Heck-Matsuda Arylations. Synthesis of β–Aryl Lactones and β–Aryl Aldehydes.

Acknowledgements: We thank the Brazilian funding agencies FAPESP, CNPq and CAPES for financial support.

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Synthesis of [Se,N]-Small Molecules: Chiral Ligands and Potentially Bioactive Compounds

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Chiral [Se,N]-Small Molecules have found growing application as ligands or catalysts in asymmetric catalysis over the past few years.[1,2] The large majority of these catalysts or ligands is derived from either readily available chiral amino alcohols or other natural sources in a few high-yielding synthetic steps.[2,3]

Additionally, the relevance of the biological and medicinal properties of organoselenium compounds is growing in a rapid pace, mainly due to their antioxidant, antitumor, antimicrobial, and antiviral properties.[4] In this context, we have developed short and efficient routes to access these type of molecules from amino acid or other natural sources, aiming to evaluate their bioactivities and/or catalytic properties. In our talk we will show our contribution in these subjects, such as the preparation of ephedrine-based diselenide (Figure 1): A promiscuous catalyst suitable to mimic the seleno-enzyme glutathione peroxidase (GPx) and to promote enantioselective C-C coupling reactions.

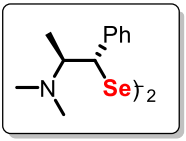

Figure 1: Ephedrine-based diselenide.

Acknowledgements: We are grateful to CNPq, INCT-Catálise, CAPES and FAPESC-Pronex for financial support.

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SLB-PL3

Porphyrins and Related Macrocycles: Synthetic Studies and Potential Applications

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Porphyrin derivatives play in Nature vital functions (*e. g*., respiration, photosynthesis, drug detoxification). Synthetic studies leading to the structural elucidation of such compounds have been carried out during the last century. For example, the syntheses of protoporphyrin IX (which forms the iron complex ruling respiration and detoxification processes) and of the photosynthetic pigment chlorophyll *a* have been reported, respectively, by Fisher in 1929 and Woodward in 1960.[1a,b] Subsequently, studies related with biosynthesis, mode of action and catabolism of such compounds and also with processes mimicking Naturehave been performed. As a result, "new chemical avenues" for such type of compounds were brought up, in relation with the needs to have better synthetic procedures and knowledge about their potential applications in several fields, mainly in Medicine.

In recent decades the Aveiro group has been involved in developing synthetic methodologies leading to new porphyrinmacrocycles and related derivatives (chlorins, bacteriochlorins, corroles). It has been shown that porphyrinmacrocycles can react under cycloaddition conditions as dienes, dienophiles and dipolarophiles. A wide range of new derivatives can be obtained in such way. Other derivatives can also be obtained by direct functionalization of the macrocycle or by substituent transformations. Potential applications for the new synthesized products have been considered. Studies have been carried out by looking at the assessment to generate reactive oxygen species and at the involvement of such species in photodynamic therapy (PDT) of cancer cells and in the photoinactivation of microorganisms; the action of metalloporphyrins as oxidative catalysts in the oxidation of organic substrates at CH(sp^3) and C(sp^2) centers, using hydrogen peroxide as the oxygen donor, has also been evaluated.[2a-d] This lecture will consider the main features of such work performed at the University of Aveiro.

Acknowledgements: Thanks are due to all students and colleagues involved in the work. Thanks are also due to the University of Aveiro and to all portuguese funding institutions (INIC, JNICT, FCT) for funding and PhD/Postdoc awarded grants. Nowadays thanks are due to Fundação para a Ciência e a Tecnologia (FCT), European Union, QREN, FEDER and COMPETE for funding the QOPNA research unit (project PEst-C/QUI/UI0062/2011) and the National NMR Network.

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New Chemical Tools to Study the Biology of Malaria

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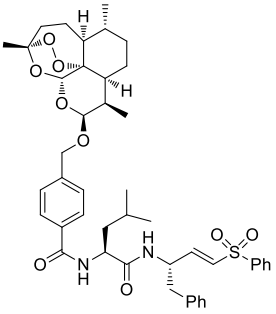
Antimalarial drugs currently in use engage a reduced number of validated targets, and their efficacy is being undermined by the spread of parasite resistance. In addition, chemical diversity among these drugs is limited, which also contributes to the emergence of cross-resistance. Antimalarial drug discovery has traditionally focused on the optimization of known lead compounds to achieve efficacious drug exposures with the lowest possible dose. Recently, ligand- and structure-based design approaches complemented by cell-based screening have been developed to identify innovative and readily synthesizable hit and lead compounds. Here, we review how chimeric compounds (e.g. **1**-**3**) have been designed and synthesized to engage different molecular targets in malaria parasites, enabling efficient elimination of parasites both in vitro and in vivo.[1-4] In addition, we will report how structure-based design and target agnostic cell-based screening led to the discovery of novel small molecules that will help to overcome our limited understanding of Plasmodium biology.[5-7]



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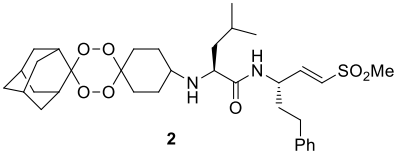

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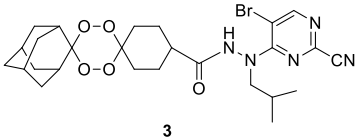

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Acknowledgements: We thank the Fundação para a Ciência e Tecnologia for financial support (PEst-OE/SAU/UI4013/2011 and REDE/1501/REM/2005)

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SLB-IOC1

Heterocycles via Pericyclic Reactions of Aza- and Diazafulvenium Methides

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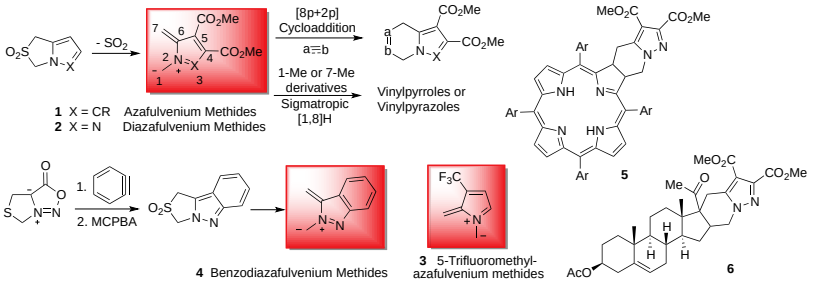
Aza- and diazafulvenium methide systems **1**-**3** are versatile building blocks for the synthesis of pyrroles and pyrazoles.[1] These extended dipoles participate in sigmatropic [1,8]H shifts and 1,7-electrocyclizations giving vinyl pyrroles and pyrazoles. Under flash vacuum pyrolysis conditions these heterocycles undergo interesting rearrangements. Aza- and diazafulvenium methides can be intercepted by dipolarophiles. The 4,5-dimethoxycarbonyl derivatives **1** and **2** act exclusively as 1,7-dipoles affording products resulting from the addition across the 1,7-positions. These 1,7-cycloadducts include chlorin and bacteriochlorin type macrocycles (*e.g.* **5**) as well as steroidal analogues (*e.g.* **6**), compounds with relevance in medicinal chemistry. In contrast with this chemical behavior, 5-trifluoromethylazafulvenium methides **3** can participate in both 1,7- and 1,3-dipolar cycloadditions. Recently, the generation and reactivity of benzodiazafulveniummethides**4** has also been described (**Scheme 1**). In this lecture, details of our contribution to the chemistry of these "higher-order" azomethine ylides and azomethine imines will be discussed.



Scheme 1: Generation and reactivity of aza- and diazafulvenium methides.

Acknowledgements: Thanks are due to FCT (PEst-C/QUI/UI0313/2011), FEDER, COMPETE and QREN for financial support.

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2,4,5-Tri(hetero)arylimidazoles: Design, Synthesis and Characterization as Novel TPA Chromophores and Optical Chemosensors

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2,4,5-Tri(hetero)aryl-imidazoles are a versatile class of compounds with a wide range of applications in diverse areas such as medicinal or materials chemistry due to their biological activity, as well their optoelectronic properties. Our earlier studies showed that the optical and thermal properties of these derivatives could be tuned by substitution of aryl groups at positions 2, 4 and 5 by 5-membered heterocycles such as thiophene and furan. This raises the potential for several innovative applications of these π-conjugated systems in nonlinear optics (*e.g.* second harmonic generators (SHG)), chemosensors, OLEDs and DNA intercalators.[1]

Recent results from our research group concerning the design, synthesis and characterization of novel 2,4,5-tri(hetero)aryl-imidazoles **1** (**Figure 1**), as two-photon absorption (TPA) chromophores and/or as optical chemosensors will be presented and discussed.

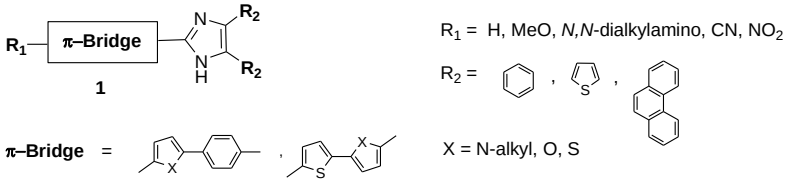

Figure 1: Structure of novel 2,4,5-tri(hetero)aryl-imidazoles.

Acknowledgements: Thank are due to *Fundação para a Ciência e Tecnologia* (Portugal) and FEDER-COMPETE for financial support through Centro de Química (PEst-C/QUI/UI0686/2011 (F-COMP-01-0124-FEDER-022716)) and Centro de Física - Universidade do Minho (Project PTDC/CTM/105597/2008 (FCOMP-01-0124-FEDER-009457)), a PhD grant to R.C.M. Ferreira (SFRH/BD/86408/2012) and a a post-doctoral grant to R.M.F. Batista (SFRH/BPD/79333/2011). The NMR spectrometer Bruker Avance III 400 is part of the National NMR Network and was purchased with funds from FCT and FEDER.

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SLB-IOC3

Sugar-based surfactants as selective antimicrobial agents: a multidisciplinary approach

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Antibiotics resistance is a global threat that encourages research on new antimicrobial molecular entities with new mechanisms of action. In this work we present the synthesis of new antimicrobial glycosides which structure differs in both glycon and aglycon components. Our previous studies on alkyl deoxy hexopyranosides of the D and L series in their α- and β-anomeric configuration have shown that high surface activity is a pre-requisite for their antimicrobial properties, and their selectivity appeared to be linked to the anomeric configuration of the sugar and to its deoxygenation pattern.[1] Hence, chemical approaches to glycon deoxygenation and structurally diverse aglycons will be presented, based on a simple but efficient methodology comprising the reaction of glycals with alcohols or their heteroanalogues, catalysed by triphenylphosphane hydrobromide. D- and L-glycosides with aglycons exhibiting alkyl chains of different size, their fluorinated or branched chain analogues, and those chains with an internal or terminal amide functionality as well as thioglycosides were synthesized. The surface activity of the aqueous solutions of several glycosides was evaluated in terms of adsorption and aggregation parameters. Compounds' bioactivity towards *Bacillus anthracis* and their acute cytotoxicity will be disclosed, revealing promising structures in view of efficacy and also of low toxicity, when compared to that of chloramphenicol. An overview of the key structural features regarding glycon and aglycon chemical composition and glycon configuration for this new family of antibiotics will be presented, highlighting the correlation of their aggregation and adsorption physical data with the antibacterial activity.

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Sulfur reloaded: New S(IV)-mediated transformations

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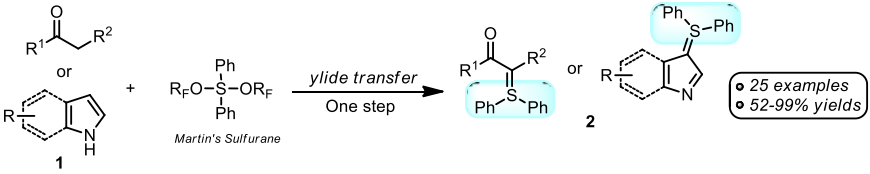
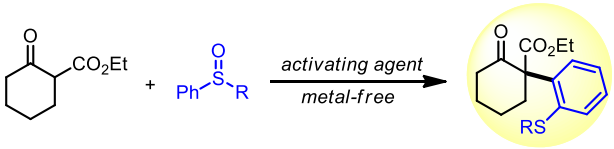
Sulfur ylides occupy a prominent place among so-called "textbook reagents" in organic chemistry.[1] Recently, they have also garnered interest as potential carbene donors for metal complexes.[2] Nevertheless, the standard syntheses of sulfur ylides are still multi(≥ 2)step procedures and applications in transition metal catalysis remain limited.[1]

We have developed a new concept of "ylide transfer" for the direct, one-step synthesis of sulfur ylides 2 from carbonyl and heteroaromatic compounds 1 (Scheme 1).[3]



Scheme 1

In this communication, results from those studies will be presented, as well as interesting applications of the ylide products in transition metal catalysis. Furthermore, an intriguing alternative pathway that results in a powerful direct arylation of carbonyl compounds (Scheme 2), as well as other recent developments, shall be discussed.[4,5]



Scheme 2

Acknowledgements: We thank the Max-Planck-Society, the Deutsche Forschungsgemeinschaft (MA 4861/4-1 and 4-2) and the Max-Planck-Institut für Kohlenforschung for support.

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SLB-IOC5

α,β-Unsaturated Diazoketones as Useful Platforms in the Synthesis of Pyrrolidine, Piperidine and Indolizidine Alkaloids

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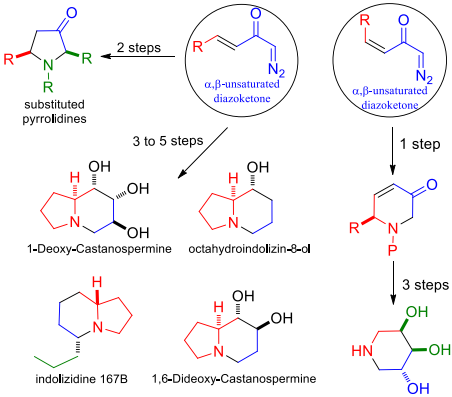
Diazocompounds are a very interesting class of compounds that can promote a wide range of reactions, such as cyclopropanations, insertion reactions, ylide formation, dimerization, and elimination and formation of ketenes by the Wolff rearrangement, among others. An interesting class of these diazocompounds is the α,β-unsaturated diazoketones,[1] which has received little attention when compared to the saturated ones due to the difficulty of its preparation by the usual existing methods. Herein, we would like to describe two new methodologies for the preparation of α,β-unsaturated diazoketones with *E* and *Z* geometry and their use as efficient platforms in the synthesis of pyrrolidines,[1] indolizidines[2,3] and piperidines (Scheme 1).



Scheme 1: α,β-unsaturated diazoketones as platforms in the synthesis of alkaloids.

Acknowledgements: We thank FAPESP and CNPq for financial support.

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Dual-acting Antimalarial Triterpenoids from an African Medicinal Plant

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Despite the efforts to eradicate malaria during the last decade, it remains a major global health problem, particularly in many of the poorest countries in the world. The increasing prevalence of drug-resistant *Plasmodium falciparum* strains is one of the greatest challenges in malaria control. In order to overcome drug-resistance, new antimalarial drugs are urgently needed.

Natural product-derived compounds have played a major role in drug discovery and development. In case of malaria drug discovery, the great significance of plant-derived drugs for the treatment of the disease is highlighted by quinine, artemisinin and their derivatives, which are currently the mainstay of the antimalarial therapy.

As part of our search for bioactive compounds from medicinal African plants, we have carried out a preliminary screening of different plants species for their antimalarial activity. *Momordica balsamina* L. (Cucurbitaceae) was found to be the most active plant. *M. balsamina,* also referred to as the balsam apple, or African pumpkin, is an extensively cultivated vegetable consumed in many tropical and subtropical regions of the world. It has also been widely used in traditional medicine in Africa to treat various diseases, mostly diabetes, and malaria symptoms.

Bioassay-guided fractionation of the methanol extract of the aerial parts of *Momordica balsamina* led to the isolation of several cucurbitane-type triterpenoids. These compounds and acylated derivatives were evaluated for their antimalarial activity against the erythrocytic stages of the *Plasmodium falciparum* chloroquine-sensitive strain 3D7 and the chloroquine-resistant clone Dd2.[1]

Evaluation of the activity of some compounds against the liver stage of *P. berghei* was also carried out[2], measuring the luminescence intensity in Huh-7 cells infected with a firefly luciferase-expressing *P. berghei* line, *Pb*GFP-Luc_{con}. Toxicity of compounds was assessed on the same cell line through the fluorescence measurement of cell confluency. Moreover, toxicity towards human cells of compounds was also investigated in the MCF-7 breast cancer cell line, showing that most of them were not toxic or exhibited weak toxicity. In blood stages of *P. falciparum,* several compounds displayed antimalarial activity, revealing some alkanoyl ester derivatives the highest antiplasmodial effects, with IC_{50} values in the nanomolar range. The highest antiplasmodial activity against the liver stages of *P. berghei* was also displayed by ester derivatives**,** with high inhibitory activity and no toxicity.

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Straightforward organic chemistry against an intricate infectious disease: new chloroquine and quinacrine analogues as dual-stage antimalarial leads

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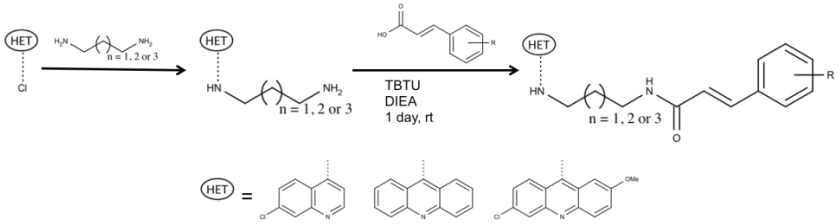
A child dies every minute from malaria. Despite this intricate infectious disease is known for millennia, and associated deaths have decreased by about 30% in Africa since 2006, eradication is far from being achieved in the near future.[1] There are well identified obstacles to malaria eradication, namely, the complexity of the malaria parasite's life cycle, widespread resistance to cheaper and most popular antimalarial drugs, and lack of efficient vaccines or multi-stage antimalarials, able to efficiently deplete liver- and blood-stage forms of *Plasmodium* parasites from the human body. Another drawback in malaria therapy is the high cost of first-line drugs, which instigates traffic of fake antimalarials.[2]

For over a decade, we have been working on the chemical modification of known drugs by means of simple and inexpensive synthetic organic chemistry, aiming at the low-cost improvement of their therapeutic properties.[3] In this connection, we have recently focused our research towards development of potential dual-action antimalarials, obtained by conjugation of cinnamic acids to aminoquinoline or acridine cores from classical antimalarial drugs (**Scheme 1**).This led to discovery of novel chloroquine and quinacrine analogues as dual-stage antimalarial leads.[4]



Scheme 1: Synthetic route towards *N*-cinnamoylated analogues of the classic antimalarials chloroquine and quinacrine.

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A Brief Saga into the Electrophilic Aromatic Substitution Mechanisms

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A discussion about the aromatic substitution mechanism, based on internal single electron transfer between the reagents and its consequences for developing new electrophilic reactions will be presented. An mechanistic continuum is proposed for explaining different reactivity and observations. This investigation lead to the development new methods for halogenation and nitration of aromatic compounds.

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