

## Chemical structure and stability of microencapsulated anthocyanins

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The development of food colorants from natural sources has been globally increased.<sup>1</sup> In this context, anthocyanins which are natural, water soluble pigments are considered suitable food pigments. Although it's potential as colorant, their industrial application is limited and a correct knowledge of the factors that govern anthocyanin's color stability seems to be decisive in terms of a putative application in food matrices.<sup>2</sup> The fact that anthocyanins co-exist in aqueous solution in a complex network of equilibrium species depending on pH is an important factor related to the color displayed by these compounds. In acidic media anthocyanins are stable while with the increase in the pH result in an unstable blue quinoidal base. Some of the color stabilization strategies rely on the formation of molecular complexes, for instance by encapsulation techniques in a carbohydrate matrix. Maltodextrins with various average molecular weights belong to the most popular capsule materials used in the food field and both hydrophobic and hydrophilic compounds have been encapsulated in maltodextrins. The encapsulated anthocyanins with maltodextrin result in a more stable product than anthocyanins alone that can be used readily as a food ingredient.<sup>3; 4</sup>

The knowledge of the nature of intermolecular interactions between the species presented in the carbohydrate-anthocyanin complexes is of fundamental importance in the understanding of the factors that determine their stability. It is therefore essential to elucidate the structure of anthocyanin-loaded particles and to clarify the mechanisms of anthocyanin immobilization in the carbohydrate matrix. The encapsulated complexes between cyanidin-3-O-glucoside (cy3glc) and maltodextrin (MDE) at different pHs are going to be investigated using a NMR spectroscopy approach. Diffusion ordered NMR spectroscopy (DOSY) and study of nuclear Overhauser effects (NOE) are going to be used to determine the selective intermolecular interactions and structure of these complexes in aqueous solution. Moreover the differences in thermal stability at three pH's (pH 2, 3 and 5) between free and encapsulated anthocyanins are going to be investigated.

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# Enzymatic Resolution of Secondary Alcohols in Miniemulsion Media

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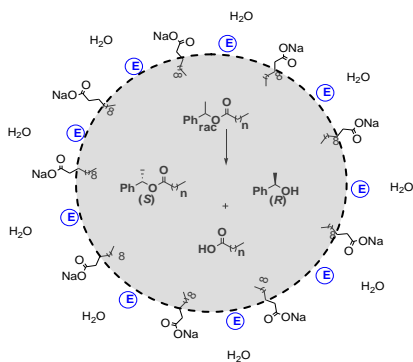
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Over the last years we have been pursuing the development of attractive, competitive and more environmentally friendly processes for the enzymatic resolution of secondary alcohols. In this line, our effort has been made on the development of new strategies for resolution of free secondary alcohols, namely by the use of more sustainable acylating agents.<sup>1</sup> More recently, we become interested on the use of miniemulsions as sustainable media for the enzymatic resolution of secondary alcohols.

Miniemulsions are characterized by a two phase system in which stable nanodroplets, between 20 and 500nm, of an organic phase are dispersed in a second continuous aqueous phase.<sup>2,3</sup> These nanodroplets are stabilized against coalescence by the addition of appropriate surfactants, which provide either electrostatic or steric stabilization. These features make miniemulsions a very appealing media for different chemical reactions.

Herein, a low temperature miniemulsion media for the preparative enzymatic resolution of 1-phenylethanol is described (**Scheme 1**). The media is characterized by the use of a miniemulsion that allows the enantioselective enzymatic hydrolysis of 1-phenylethyl alkanoates at low temperatures. The central feature of this methodology is the low temperature miniemulsion system that drives the reaction equilibrium by the precipitation of one of the products. The preparative miniemulsion enzymatic reaction of 1-phenylethyl alkanoates at 4°C allowed the preparation of both free enantiomers in good yields and enantiomeric excess.



**Scheme 1:** Miniemulsion methodology for the enzymatic resolution of 1-phenylethanol.

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## The acid-catalysed reaction of 2-hydroxychalcones with carbon acids

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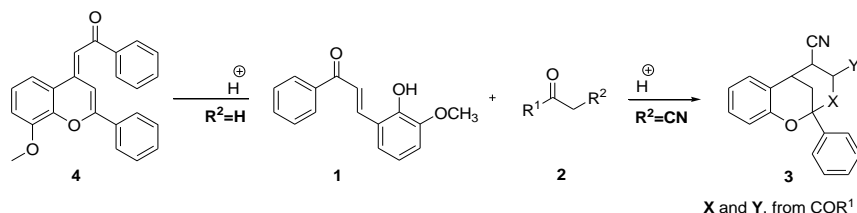
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Chalcones have been used as important precursors of the chromene scaffold, present in a wide variety of compounds including natural products. Important pharmacological properties have been identified and this nucleus has been an inspiration for the synthesis of analogues, since some derivatives exhibit remarkable biological activities namely anticancer, anti-inflammatory, antioxidant, antitubercular, anti-microbial and anti-HIV.<sup>1,2</sup>

Chalcones can be prepared by the Aldol condensation of a ketone and an aldehyde, a reaction that is usually performed in aqueous basic media. The condensation of an active methylene compound with salicylaldehydes in the presence of base catalysis is also a well-known reaction that directly leads to the formation of 2-imino or 2-oxo-2*H*-chromenes.<sup>3,4</sup> Previous experimental results in our research group, on the reactivity of  $\alpha,\beta$ -unsaturated carbonyl compounds, revealed that they react with carbon acid derivatives, leading to distinct chromene-based structures. The careful control of experimental conditions and the nature of the carbon acid proved to be crucial for the product isolated.

In this work, a study on the reactivity of the 2-hydroxychalcones **1** with different carbon acid derivatives **2**, in the presence of acid catalysis (**Scheme 1**), will be presented. A proposal for the mechanistic pathways leading to the formation of the corresponding products **3** and **4** will also be discussed.



**Scheme 1:** Reaction of chalcone **1** with carbon acids **2**.

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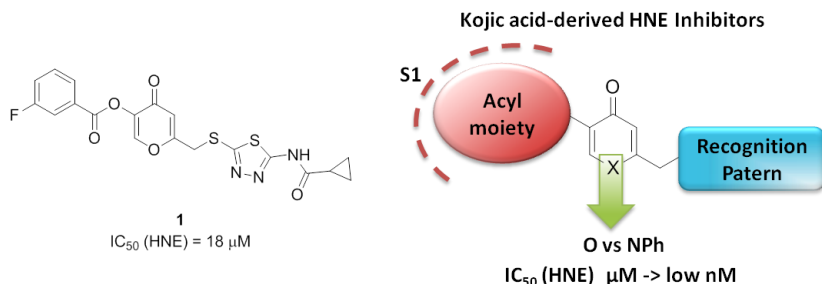
## Hit-to-Lead Optimization of kojic Acid Derivatives toward COPD Drug Discovery

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Combination of emphysema and chronic asthmatic bronchitis — a deadly duo known as chronic obstructive pulmonary disease (COPD) affects millions of people worldwide that find distressingly difficult to breathe. The primary cause of COPD is tobacco smoke but other risk factors include air pollution or occupational dusts and chemicals. COPD is not curable and the available treatment only helps to control its symptoms. Therefore, COPD-related deaths are projected to increase dramatically, being COPD predicted by WHO to become the third leading cause of death by 2030.<sup>1</sup> Human Neutrophil Elastase (HNE) is a serine protease which plays a major role through COPD inflammatory process wherein due to an imbalance between protease and anti-protease, an excess of HNE is produced hydrolyzing elastin, the structural protein which gives the lungs their elasticity.<sup>2</sup> Recently we developed a virtual screening protocol toward HNE hit generation that led us to the kojic derivative **1** (Figure 1),<sup>3</sup> which is a 18  $\mu\text{M}$  acyl-enzyme inhibitor that showed to be selective for HNE when compared with parent proteases. Hence we envisaged a lead optimization campaign toward an activity and drugability gain along the kojic acid scaffold, which was the aim of the present work (Figure 1). Kojic acid derivatives were synthesized with different small and hydrophobic ester moieties as it is preferred for HNE S1 pocket recognition, while we introduced several thioether-linked building blocks as recognition pattern on the opposite counterpart of the acylating function. On the other hand we studied the effect of having a pyrone versus an aryl- $\gamma$ -pyridone scaffold. Lead optimization protocol allowed the synthesis of very promising compounds with activities in the nM range with good selectivity profiles.



**Figure 1**

**Acknowledgements:** We thank the Fundação para a Ciência e Tecnologia for financial support, Pest-OE/SAL/UI4013/2011, SFRH/BPD/64265/2009 (SDL).

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# New antimicrobial structures with anti-ageing potential: an efficient synthesis towards 2-deoxy glycosides and their thio analogues

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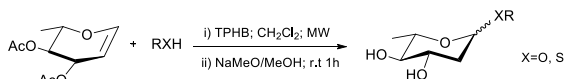
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Sugar-based surfactants are a very appealing class of compounds due to their low toxicity and their synthesis from renewable resources. Alkyl deoxy-*arabino*-hexopyranosides with a potent antimicrobial activity in several *Bacillus* species have been previously described by our research group.<sup>1</sup> Aiming at a better insight to the relationship between these lead structures and their bioactivity, new alkyl 2-deoxyglycosides as well as their thio analogues were synthesized. Their preparation was accomplished by reaction of 1,5-anhydro-3,4-di-O-acetyl-2,6-dideoxy-L-*arabino*-hex-1-enitol (3,4-di-O-acetyl-6-deoxy-L-glucal) or its benzylated analogue with the corresponding alcohol or thiol, using triphenylphosphane hydrobromide (TPHB) as catalyst, followed by deprotection (**Scheme 1**). The previously reported reaction conditions<sup>2</sup> were optimized and microwave assisted reactions were run for the first time to synthesize the deoxy thio glycosides. 3,4-Di-O-benzyl-6-deoxy-L-glucal revealed to be the most efficient starting material, as it diminished the formation of the Ferrier secondary product, and its synthesis will also be presented.

The antimicrobial activity of these newly synthesized compounds was studied on *Bacillus* species, namely *B. cereus* and *B. anthracis*, and some of them showed a remarkable and reproducible activity against the latter.

Moreover, infections in elderly populations are known to be not only more frequent but also more severe, being this susceptibility often related to neurodegenerative diseases such as dementia and Alzheimer's.<sup>3</sup> A preliminary study assessing the anti-amyloidogenic potential of these 2-deoxy glycosides has previously demonstrated that these compounds interact with soluble cystatin B, opening a new window into a new line of investigation, pertaining to antibiotic compounds showing neuroprotective activity. An investigation to check the ability of these new structures to protect cells against A $\beta$  induced toxicity is currently on going and will also be presented.



**Scheme 1:** Synthesis of alkyl deoxy-*arabino*-hexopyranosides using TPHB as catalyst.

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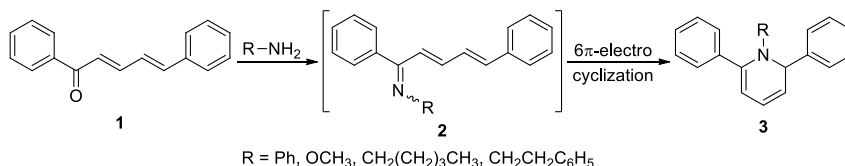
# Synthesis of *N*-substituted 1,2-dihydropyridines by 6 $\pi$ -electrocyclisation of (*E,E*)-cinnamylidene acetophenones

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From the five theoretically possible isomeric dihydropyridines, the 1,2- or the 1,4-dihydro structure are the most commonly found in known dihydropyridines.<sup>1</sup> The 1,4-dihydropyridines are known to possess a wide range of biological and pharmacological actions namely as calcium-channel modulating agents in the treatment of cardiovascular disease; as multidrug-resistance-reversing agents in cancer chemotherapy and as antimycobacterial and anticonvulsant agents.<sup>2</sup> The less studied 1,2-dihydropyridines consist of an important scaffold for the preparation of 2-azabicyclo[2.2.2]octanes (isoquinuclidines).<sup>3</sup> The isoquinuclidine ring system is widely found in natural products such as ibogaine and dioscorine alkaloids, which have a large spectrum of interesting biological properties.<sup>3</sup> Because of the lack of general methods for the regioselective synthesis of highly functionalised 1,2-dihydropyridines, their potential remains largely unexplored.<sup>4</sup> Our group has recently started a project considering the synthesis of this templates using (*E,E*)-cinnamylidene acetophenones **1** (Scheme 1) as versatile starting materials. (*E,E*)-cinnamylidene acetophenones **1** are a major group of  $\alpha,\beta,\gamma,\delta$ -diunsaturated ketones, widely used in a variety of synthetic transformations namely by our research group. In the present communication we describe a novel one-pot synthetic route to prepare *N*-substituted 1,2-dihydropyridines **3** using compound **1** as starting material and several primary amines. This reaction proceeds by forming a ketimine intermediate **2** that through a 6 $\pi$ -electrocyclisation afforded the desired product **3** in moderate yields.



**Scheme 1:** Synthesis of *N*-substituted 1,2-dihydropyridines **3** via a 6 $\pi$ -electrocyclisation of ketimine **2**.

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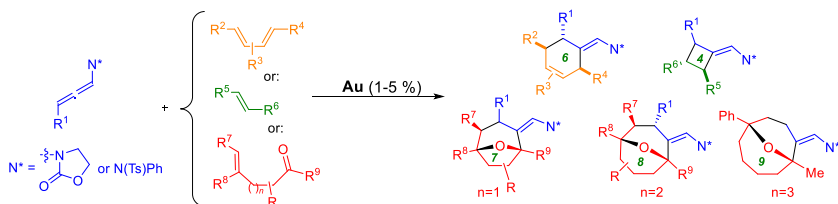
# Gold (I) catalyzed intermolecular cycloadditions of allenamides: a simple route to small and medium sized carbocycles

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In recent years there have been extraordinary advances in the development of new Au-catalyzed processes. In this context, our group demonstrated in 2009 the possibility of using allenes in intramolecular (4 + 2) and (4 + 3) cycloadditions of allenedienes, including their enantioselective versions.<sup>1</sup> Herein, we describe our efforts in the development of intermolecular Au-catalyzed cycloadditions with allenic scaffolds. In particular, we will demonstrate that the use of allenamides, a particularly accessible and versatile type of allenic scaffold, allowed the discovery of highly selective and even enantioselective gold-catalyzed (4 + 2) cycloadditions to 1,3-dienes.<sup>2</sup> The detection of minor side products resulting from a (2 + 2) cycloaddition between the allenamide and one of the double bonds of the diene, prompted us to specifically pursued the development of a gold-catalyzed intermolecular (2 + 2) cycloaddition, which could be achieved using appropriate alkenes and a phosphite-gold catalyst.<sup>3</sup> Finally, very recent examples of a simple and highly versatile cascade cycloaddition between allenamides and carbonyl-tethered alkenes, including several enantioselective examples, will be also described. This method enables a straightforward and highly efficient entry to oxa-bridged seven-, eight- and even nine-membered rings.<sup>4</sup>



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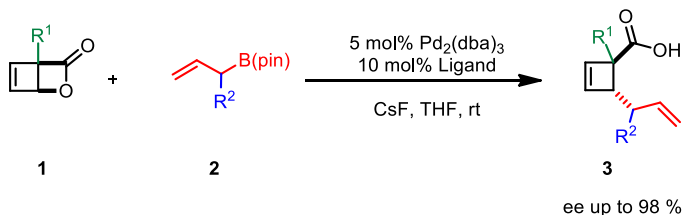
## Regio- and Enantioselective Cyclobutene Allylations

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Palladium catalysed asymmetric allylic alkylation (AAA) is a powerful synthetic method for the preparation of optically active compounds.<sup>1</sup> Recently, our laboratory has focused on the palladium-catalysed reactions of bicyclic lactone **1** with stabilized (“soft”) nucleophiles to generate highly functionalised cyclobutenes with impressive diastero- and enantioselectivities.<sup>2,3</sup> We have now investigated the behaviour of this system in the presence of nonstabilized (“hard”) nucleophiles. In this presentation, we report our preliminary results on the catalytic, asymmetric regioselective allylation of lactone **1** with allyl boronates **2** (**Scheme 1**) as well as exploratory mechanistic studies.<sup>4</sup>



**Scheme 1:** Pd-catalyzed allylation of lactones **1** with allyl pinacol boranes **2**

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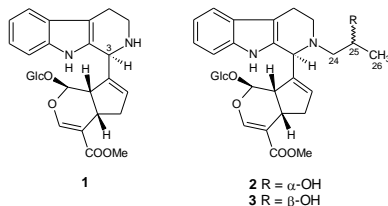
## Two new monoterpene indole alkaloids from *Psychotria umbellata* Vell.

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*Psychotria* genus (Rubiaceae) is divided in three subgenera: *Psychotria* (pantropical), *Tetramerae* (species of Africa and Madagascar) and *Heteropsychotria* (neotropical). The latest subgenus is chemically characterized by monoterpene indole alkaloids (MIAs). In a previous study, it was reported the isolation of an unusual MIA from *P. umbellata*, named psychollatine (**1**), formed by the condensation of a geniposide derivative with triptamine.<sup>1</sup> Considering it, in the present study it is reported the isolation and characterization of two new psychollatine derivatives from *P. umbellata*. The ethanol extract of the leaves of the plant was dissolved in HCl 2% and partitioned with CH<sub>2</sub>Cl<sub>2</sub>. Later, the acid phase was basified and re-partitioned with CH<sub>2</sub>Cl<sub>2</sub>, resulting in the alkaloid fraction (766 mg). This fraction was submitted to VCC using CHCl<sub>3</sub>/MeOH as eluent. One of the subfraction was purified by PTLC using CHCl<sub>3</sub>/MeOH (85:15) in the presence of NH<sub>3</sub> vapor as eluent, resulting in compounds **2** (43 mg) and **3** (29 mg). Both **2** and **3** displayed pseudo-molecular ions at *m/z* [M + H]<sup>+</sup> 587 in the CIMS spectra, matching with C<sub>30</sub>H<sub>38</sub>N<sub>2</sub>O<sub>10</sub>. <sup>13</sup>C NMR (100 MHz) confirmed the presence of 30 carbon atoms and the proton-bearing carbons were assigned from HMQC spectra. Both alkaloids displayed a <sup>1</sup>H NMR (400 MHz) pattern of tetrahydro-β-carboline glucosidic MIA, similarly to **1**. Comparing **2** and **3** to **1**, is verified that their mass spectra are compatible with an additional –C<sub>3</sub>H<sub>6</sub>O substituent. For **2** and **3**, the <sup>1</sup>H-<sup>1</sup>H COSY spectrum showed correlations of H-25 with H-24a, H-24b, and 3H-26. Taking together these <sup>1</sup>H-<sup>1</sup>H COSY correlations with the <sup>13</sup>C NMR chemical shifts displayed by C-25, and the multiplicity of the <sup>1</sup>H NMR signals attributed to H-25, it is possible to assign that C-25 is bound to an oxygen, a methyl, and a methylene groups, consisting of an isopropanol moiety. Moreover, based on the analyses of the <sup>1</sup>H and <sup>13</sup>C NMR spectra, it is possible to suggest that the C-24 is bound to the N-4 of the **1** nucleus in both compounds. In order to confirm the structures attributed for alkaloids **2** and **3**, these two compounds were synthesized with racemic propylenoxide and psychollatine. The two resulting compounds displayed the same R<sub>f</sub> on TLC that products **2** and **3** and similar <sup>1</sup>H NMR spectra. In addition, to find the relative configuration at C-25, the synthesis was performed using the S-isomer of propylenoxide, demonstrating that compound **2** is N<sup>R</sup>-[1-(2-α-hydroxypropyl)]-psychollatine and compound **3** is N<sup>R</sup>-[1-(2-β-hydroxypropyl)]-psychollatine.



**Acknowledgements:** We thank to CNPq, CAPES and FAPERGS for their financial support.

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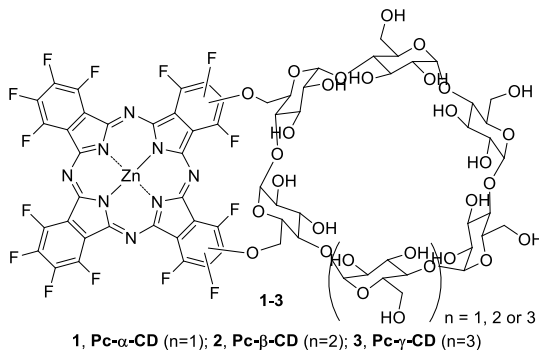
## Synthesis, photophysical and photodynamic activities of amphiphilic phthalocyanine-cyclodextrin conjugates

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Phthalocyanines (Pcs) and cyclodextrins (CDs) have been intensively studied due to their applications in many scientific fields, being their use as photosensitizers (PSs) in photodynamic therapy (PDT) one of the most promising.<sup>1</sup> PDT uses a blend of visible light, oxygen and a PS to cause an efficient and selective methodology for the treatment of several diseases.<sup>2</sup> Three novel Pcs conjugated with  $\alpha$ -,  $\beta$ - and  $\gamma$ -CDs have been prepared and assessed for application as new PS agents (**Figure 1**) by photophysical, photochemical and *in vitro* photobiological studies. The simple nucleophilic substitution of two  $\beta$ -fluorine atoms on the hexadecafluorophthalocyaninato zinc(II) (**PcF<sub>16</sub>**) enabled the preparation of these hybrids. The conjugates **Pc- $\alpha$ -CD** and **Pc- $\gamma$ -CD** demonstrated high efficiency to interact with human serum albumin, to generate singlet oxygen and were highly phototoxic against UM-UC-3 human bladder cancer cells. The lower photodynamic activity of the **Pc- $\beta$ -CD** can be attributed to its higher aggregation tendency, leading to a lower efficiency to generate reactive oxygen species inside the cells. The promising photoactivity of **Pc- $\alpha$ -CD** and **Pc- $\gamma$ -CD** ensure the potential candidacy as PDT drugs.



**Figure 1:** Representation of the Pc-CD dyads 1-3.

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# Iminoboronates: A New Strategy for Reversible Protein Modification

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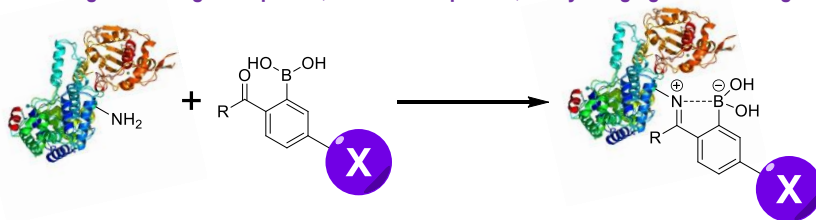
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Proteins are biomolecules that carry out the majority of cell's functions, acting as their structural blocks, as catalysts in all processes concerning cellular metabolism, and as regulators of cell cycle, differentiation, growth, division, motility, death, among others.<sup>1</sup> Furthermore, therapeutic peptides or proteins show crucial importance in some pathologies, namely, insulin, GNRH/LHRH agonists, sandostatin, calcitonin or platelet aggregation inhibitors. However, since these molecules are unstable to some conditions, peptide and protein enhancement technologies are being developed in order to have more suitable delivery systems.<sup>2</sup> Selective modification of native proteins is one of the approaches to change the protein's properties without shifting its function or natural structure.

We present a new strategy to modify the lysine's  $\epsilon$ -amino group and the protein's N-terminal, based on the formation of stable iminoboronates in aqueous media. The modification of these amine groups can be reverted upon the addition of fructose, dopamine, or glutathione.<sup>3</sup> Moreover, derivatives of these modifying agents were synthesized in order to confer some biological properties that the biomolecules didn't possess naturally, namely, enhanced pharmacokinetics (PEGylation), fluorescence or even the ability of conjugation with drugs (**Figure 1**).

**X being: Bioorthogonal species, Fluorescent probes, PEGylating agents and Drugs**



**Figure 1:** Selective modification of native proteins using derivatives of 2-carbonylbenzeneboronic acid (R=H – formyl derivative, R=CH<sub>3</sub> – acetyl derivative)

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## New 2-amino-4-functionalized Cyclopentenones from 2-furaldehyde via a One-pot Method

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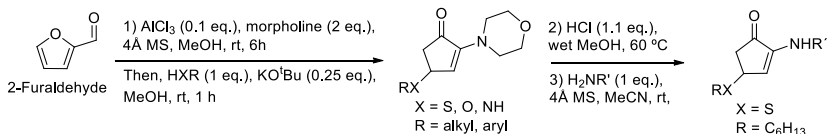
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Functionalized cyclopentenones are amongst the most valuable precursors available for synthesis of active biomolecules and derivatives. In particular, diamino cyclopentenones are useful for the synthesis of Agelastatin A<sup>1</sup> whereas 2-aza-cyclopentenones can be useful for the synthesis of (–)-Cephalotaxine,<sup>2</sup> Palau'amine<sup>3</sup> and (+)-Nakadomarin.<sup>4</sup> However, most syntheses towards functionalized 2-aza-cyclopentenones remain multi-step strategies. Thus, we were interested in reports of a one step transformation in the presence of Lewis acids that has afforded *trans*-diamino cyclopentenones from 2-furaldehyde in high yields.<sup>1b</sup> This method has been expanded to obtain 4-aminocyclopentenones via the aza-Piancatelli rearrangement.<sup>5</sup>

We have reported<sup>6</sup> the conversion of 2-furaldehyde into bifunctionalized cyclopentenones via 1,4-addition of nucleophiles to intermediate *trans*-diamino cyclopentenones, coupled with  $\beta$ -elimination. Our studies have established a new one-pot method that afforded a variety of functionalized 2-amino-4-functionalized cyclopentenones with a variety of nucleophiles comprising mostly thiols as well as amines and alkoxides with yields in the 60–80% range (**Scheme 1**). Further enamine modification was also achieved under mild conditions.



**Scheme 1:** Synthesis of new 2,4-bifunctionalized cyclopentenones from 2-furaldehyde.

**Acknowledgements:** We thank the Fundação para a Ciência e a Tecnologia and FEDER (Ref. SFRH/BD/31678/2006 and POCI/QUI/56582/2004)

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## Organocatalytic Asymmetric Synthesis of Cyclopropylphosphonates

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Phosphonates have a wide range of applications in medicine, agriculture and materials science. Their bioactivity derives from their close structural similarity to the phosphates that occur widely in living organisms and to carboxylic acids of which they are isosters. If there is a chiral centre present in the molecule, its configuration is often critical for activity. There are a few cyclopropylphosphonates with proven biological activity: insecticidal, anti-malarial, anti-viral, enzyme inhibitors and glutamate metabotropic receptor agonists. Aminocyclopropylphosphonates are constrained analogues of amino acids, and have been used for the synthesis of interesting peptidomimetics. Some aminocyclopropylphosphonates are also known to be potent inhibitors of HCV NS3 protease, a promising target for therapy against the hepatitis C virus, which presently is estimated to infect 170 million people worldwide.<sup>1</sup> As a follow-up on our interest in developing chiral methodology for the synthesis of biologically active phosphonates,<sup>2</sup> we have now developed a novel organocatalytic method to synthesize chiral  $\alpha$ -cyclopropylphosphonates based on a domino process. In this communication we present the results obtained and preliminary results on synthetic applications of the new methodology.

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## Catalytic Asymmetric Benzidine Rearrangement

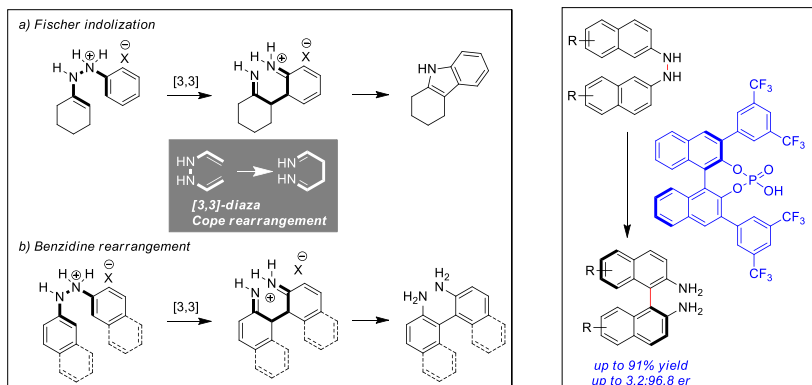
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The [3,3]-diaz Cope rearrangement is a powerful synthetic motif that can be utilized to generate a C–C bond at the expense of a N–N bond. It forms the basis of important and fundamental acid catalyzed transformations such as the Fischer indolization and the benzidine rearrangement (**Figure 1**).<sup>1</sup> Recently, our group has established the first catalytic asymmetric variant of the Fischer indolization. In light of the mechanistic similarities between the two reactions, we set up a program towards developing an asymmetric benzidine rearrangement. Such a transformation may find utility in the synthesis of highly useful chiral biaryls such as 1,1'-binaphthyl-2,2'-diamine (BINAM).

A Brønsted acid catalyzed asymmetric benzidine rearrangement was developed, providing different electronically and structurally diverse axially chiral 2,2'-binaphthyl diamine (BINAM) derivatives with high enantioselectivity.<sup>2</sup>



**Figure 1:** The diaza Cope rearrangement and its synthetic utilization.

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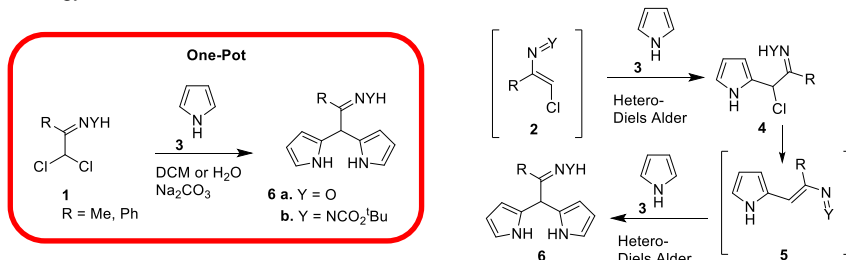
## Novel synthesis of dipyrromethanes via hetero-Diels-Alder reaction of azo- and nitrosoalkenes with pyrrole

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Porphyrins and 4,4-difluoro-4-bora-3a,4a-diaza-s-indacenes (BODIPY) are a class of compounds with great potential, namely as sensitizers in multiple applications.<sup>1</sup> Dipyrromethanes are important building blocks in the synthesis of these compounds. This has led to an increasing interest in developing new synthetic methods to obtain novel *meso* substituted dipyrromethanes.<sup>2</sup> Generally, acids or Lewis acids are necessary to catalyze the 5-substituted dipyrromethane synthesis. However, polymerization of pyrrole and the formation of by-products require carefully controlled reaction conditions. In this communication, we will present a new acid free catalyzed one-pot synthetic strategy for 5-substituted dipyrromethanes (e.g compounds **6a** and **6b**, **Scheme 1**). Hetero-Diels-Alder reactions of azoalkenes and nitrosoalkenes are extremely important in preparing heterocyclic compounds containing nitrogen such 1,2-oxazines, pyridazines and isoxazolines.<sup>3</sup> Herein, we present a novel *bis*-hetero-Diels-Alder reaction with azo- and nitrosoalkenes, giving *meso* functionalized dipyrromethanes. Details of this synthetic strategy will be disclosed.



**Scheme 1:** Synthetic route to 5-substituted dipyrromethanes from hydrazones or oximes and pyrrole.

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# Dirhodium(II) Complexes Derived from Natural Amino Acids as Catalysts in Aqueous Asymmetric Intramolecular C-H Insertion of $\alpha$ -Diazo Acetamides

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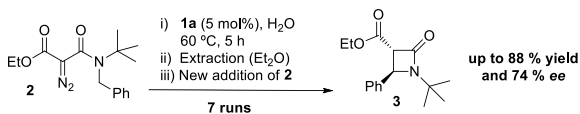
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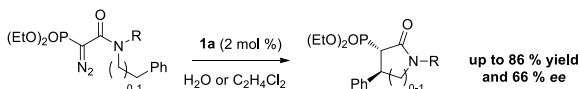
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The use of dirhodium stabilized carbenes in intramolecular C-H insertion of  $\alpha$ -diazo substrates is a powerful methodology for the synthesis of highly valuable compounds.<sup>1</sup> The extrapolation of intramolecular C-H insertion in organic solvents to aqueous medium indicates that the success of the transformation is dependent on the hydrophobic nature of the metalocarbene formed.<sup>2</sup>

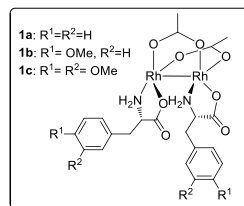
Recently, we have demonstrated the preparation of a new type of homochiral dirhodium complexes based on natural amino acids (**1a-c**).<sup>3</sup> Such complexes can be either isolated or formed in situ by ligand exchange of dirhodium(II) tetraacetate. These new complexes were tested in the aqueous asymmetric intramolecular C-H insertion of  $\alpha$ -diazo acetamides providing the corresponding lactams in good yields and moderate enantioselectivities. The catalytic system could be reused six times by simple extraction of the reaction product with ethyl ether (**Scheme 1**). The asymmetric preparation of  $\alpha$ -phosphono- $\beta$ -lactams in water and dichloroethane was achieved in up to 66 % ee (**Scheme 2**), making this the most enantioselective method for the preparation of such compounds. The reaction scope regarding the amide substituents and  $\alpha$ -substituent influence was also studied.



**Scheme 1**



**Scheme 2**



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