

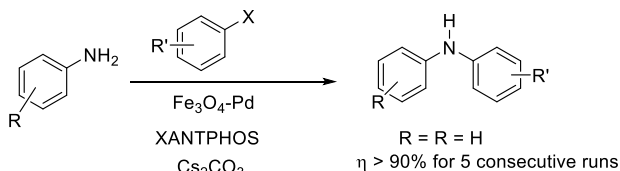
A Recyclable Ferrite–Pd Magnetic Nanocatalyst for the Buchwald-Hartwig reaction

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Functionalized magnetic nanoparticles (MNPs) are heterogeneous catalyst supports which have emerged as viable alternatives to conventional materials because they are robust, inert, inexpensive, reusable, and recyclable using a simple magnet.¹ Magnetite is a well-known material, also known as ferrite (Fe_3O_4), which has been used as a versatile support for functionalization of metals, organocatalyst, and chiral catalysts.² Arylamines are compounds of increasing importance as evidenced by its application on the synthesis of artificial dyes, or the synthesis of biologically active compounds such as pharmaceuticals and agrochemicals. The homogeneous palladium-catalyzed aromatic aminations independently developed by Buchwald^{3a} and Hartwig^{3b} were a great success because of their wide range of applicability under relatively mild conditions. Here we report the immobilization of palladium on the surface of magnetite, and the catalyst thus prepared $\text{Fe}_3\text{O}_4\text{-Pd}$ was successively applied in the arylation of amines and amides (Scheme 1).



Scheme 1: Buchwald-Hartwig reaction catalyzed by functionalized magnetic nanoparticles, $\text{Fe}_3\text{O}_4\text{-Pd}$.

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Developments in Enantioselective Immobilized BINOL-based Tandem Reactions

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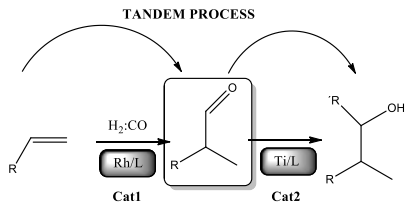
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The synthesis of chiral compounds is a challenging area of contemporary synthetic organic chemistry due to the broad applications of synthetic chiral molecules in medicine and materials. This is the main reason for the increased interest in developing new asymmetric catalytic process. Based on amplified environmental concerns, asymmetric tandem reactions emerged as a powerful strategy to improve the synthetic efficiency and reduce the amounts of solvents. On this context, hydroformylation¹ is considered a key tool for the one-step transformation of olefins into valuable aldehydes, which can be transformed into high value compounds in a sequential process. Moreover, immobilization of chiral ligands into solid supports allows the conjugation of the selectivity of homogeneous catalytic processes with the easy recovery of the catalyst characteristic of heterogeneous catalysts.²



In this communication we present the recent developments of immobilized BINOL-based ligands and its application in Tandem hydroformylation/hydrocyanation or alkylation reactions. A comparative study between homogeneous and heterogenized catalyst will be presented and discussed.

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Biological activities of oxygen and nitrogen heterocyclic compounds

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Oxygen and nitrogen heterocyclic compounds often display a wide array of biological activities, being for example very active antioxidants, antifungal, antitumor, antiviral, cannabinoid agonists and anti-inflammatory¹. In this context, we review some of the more relevant structures, such as chromone and pyrazole derivatives (Fig. 1), which have biological activities that render these molecules excellent scaffolds for extremely active drugs. After this introduction, we report the biological activities of oxygen heterocyclic compounds synthesized by our group. *In vitro* cytotoxicity was assessed by the MTT method and anticholinesterase activity by a modification of the Ellman method². Most of the compounds tested were extremely active against HeLa tumor cell line, both in lag and in log phases of growth. However, they were equally toxic to Vero non tumor reference cell line, which means that further structural modifications need to be carried out if these molecules are meant to be used as chemotherapeutic agents. Concerning anticholinesterase activity, results were extremely favourable, since several of the compounds tested were very strong inhibitors of the enzyme. Computational docking using the FlexScreen program suggested that interaction with the enzyme is mainly at the peripheral anionic site of the acetylcholinesterase active site gorge. The excellent results obtained for anticholinesterase activity indicate that some of these compounds have potential as drugs in the treatment of Alzheimer's disease. Future structural modifications, directed by indications provided by computer-guided approaches, will be tested by *in vitro* bioassays in order to enhance both activity and selectivity.

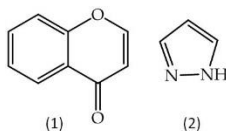


Figure 1: (1) Chromone and (2) pyrazole.

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New syntheses of potential biologically active xanthenes and benzoxanthenes

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Xanthenes have a rather restricted occurrence among higher plants, being found almost exclusively in *Guttiferae* and *Gentianaceae*.¹ Natural and synthetic xanthone derivatives have been described as exhibiting several important biological properties, such as anti-tumor,^{2a} anti-inflammatory^{2b} and antioxidant^{2c} activities which make them attractive to the pharmaceutical industry.

The synthesis of xanthenes, adequately functionalized for a specific application, is a challenging task. In this presentation, will be disclosed our recent studies with this unique family of compounds, namely the one-pot photoinduced electrocycloislation of (*E*)-3-styrylflavones **1** and *in situ* oxidation of cycloadducts to give 5-phenyl-7*H*-benzo[*c*]xanthen-7-one derivatives **2**,^{3a} and aromatization studies of (*E*)-3-aryl-4-benzylidene-8-hydroxy-3,4-dihydro-1*H*-xanthen-1,9(2*H*)-diones **3**^{3b} into 4-benzyl-1,8-dihydroxy-3-phenyl-9*H*-xanthen-9-one derivatives **4** (Figure 1).

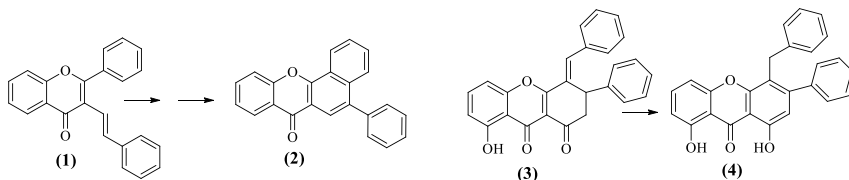


Figure 1: Xanthone derivatives structure.

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Synthesis of 1-vinylidene-naphthofurans: A thermally reversible photochromic system that colours only when adsorbed on silica gel

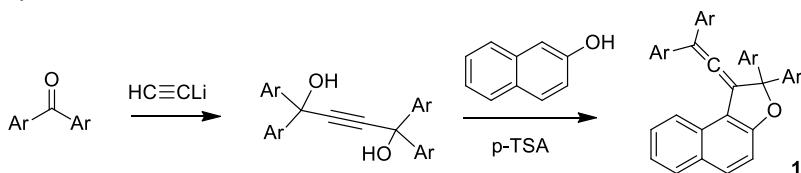
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A set of new 1-vinylidene-1,2-dihydro-naphtho[2,1-*b*]furans were unexpectedly obtained in the reaction of 2-naphthol with easily obtained 1,1,4,4-tetraarylbut-2-yne-1,4-diols at room temperature in the presence of a catalytic amount of *p*-toluenesulfonic acid (**Scheme 1**). A mechanism for the formation of this allenic compound was proposed involving ether formation, Claisen rearrangement, enolization and dehydration. The reaction is compatible with different substituents in the aromatic ketone and afforded naphthofurans **1a-c** in 19-47% yield.



Scheme 1: Synthesis of 1-vinylidenenaphtho[2,1-*b*]furans **1** from aromatic ketones.

Surprisingly, when adsorbed in silica gel, these new compounds exhibit photochromism at room temperature while not in solution and in the solid state. UV or sunlight irradiation leads, in few seconds, to the formation of intense pink/violet to green colours that bleach completely in few minutes in the dark (**Scheme 2**). This phenomenon is reproducible and can be repeated several times without any sign of degradation. These new compounds also exhibit reversible acidochromic properties in solution: addition of trifluoroacetic acid leads to the formation of an intense violet colour that return immediately to the uncoloured initial state upon addition of NET_3 .



Scheme 2: Photochromic equilibrium for new 1-vinylidene-naphthofuran **1a** (Ar=Ph) and photographs of silica gel doped with this compound before and after UV irradiation (365 nm)

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Electronic Communication in Linear Oligo(azobenzene) Radical Anions

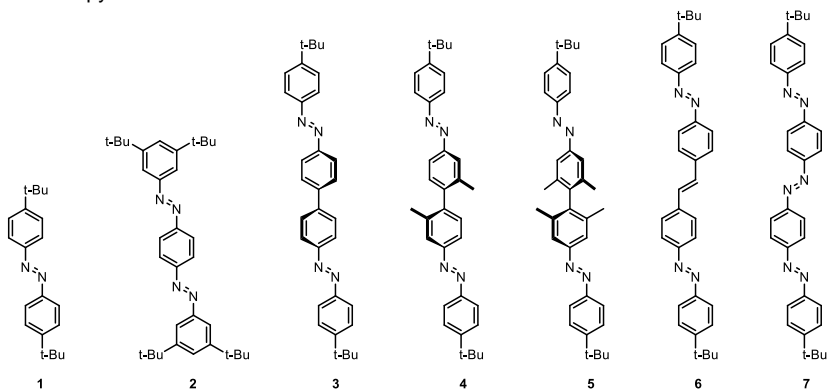
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The azobenzene molecular unit has been extensively studied in the recent past due to the potential use of its *cis-trans* photoisomerization reaction in optical switches, information storage or mechanical devices. Although the photochemistry of the azo group has received enormous attention, the potential use of azobenzene system as charge-carrier in organic devices has been seldom addressed in literature. The ability to transport charge depends on the efficiency with which the charge moves within the π -conjugated system. With this purpose, the use of mixed-valence chemistry offers a unique tool to study how the localization of charge in organic radical ions depends on the structural and chemical features.¹

Although the photochemistry of the azo group has received enormous attention, the potential use of azobenzene systems as charge-carriers in organic devices has been seldom addressed in the literature. In this context, it is of significant interest to understand how the chemical structure affects the electronic coupling in negatively charged azobenzene oligomers. We studied in this work the radical anions of seven azobenzene oligomers, where the charge is mainly centered in the diazo groups, by optical and EPR spectroscopy.



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Isolation and Identification of Impurities in Tetracycline Derivatives

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Identification, qualification and quantification of impurities are critical tools for assessing the safety and quality of pharmaceutical drug substances. In order to market a drug, active pharmaceutical ingredients (API) the manufacturer should ensure that the different classes of impurities due of synthesis and degradation are addressed and adequately controlled in the drug substance. Cipan produces API's for more than fifty years and has been always committed to respond to the increasingly demanding guidances¹ on API's production and qualification. The identification and characterization of impurities is of utmost importance in today's regulatory environment and a *sine-qua-on* capability if one wants to sell in the most regulated markets.

The focus of this work is to develop an efficient process of synthesis of possible impurities of tetracycline's derivatives produced by Cipan (Figure 1).

Synthesis of some impurities and/or degradation products of tetracycline derivatives produced will be described. These include epimers and some other potential impurities. The synthesized compounds as well as the corresponding intermediates were characterized.

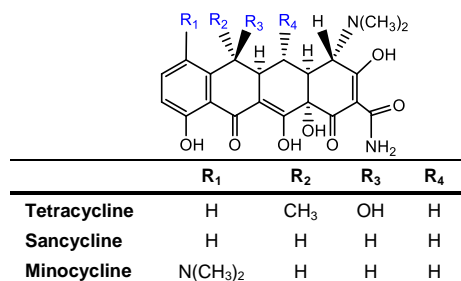


Figure 1: Chemical structures of Tetracycline derivatives

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New Chemical Processes with Bismuth(III) Salts: Applications of Bismuth(III) Reagents and Catalysts to Steroid and Terpenoid Chemistry

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Steroids and terpenes constitute a large and structurally diverse family of natural products and are considered important scaffolds for the synthesis of molecules of pharmaceutical interest.¹

The growing relevance of green and sustainable chemistry and the application of its guiding principles to the development of new reactions and chemical processes is changing the face of chemistry.² Bismuth(III) salts are known for their low toxicity, making them potential valuable reagents for large-scale synthesis, which becomes more obvious when dealing with products such as active pharmaceutical ingredients or synthetic intermediates.³

In this communication, the work developed in our lab in the application of bismuth(III) salts as reagents and/or catalyst to the chemistry of steroids and terpenoids is presented. The reactivity of Bi(III) salts towards epoxysteroids has been studied, leading to the novel reaction conditions for the Ritter reaction.⁴ Modulating these reaction conditions, new bismuth-based processes for the synthesis of either β -substituted alcohols⁵ or olefinic 18-nor and 18,19-dinorsteroids have been developed.⁶ Bismuth(III) salts were found suitable catalysts for rearrangement reactions and a new Bi(III)-based process for the Wagner-Meerwein rearrangement of lupanes have been reported.⁷ On the other hand, a novel reaction for direct synthesis of 12-oxo-oleanolic acid derivatives have been developed starting from the corresponding γ -hydroxylactones.⁸ A high value catalytic process for the selective cleavage of the C17-dihydroxyacetone side chain of corticosteroids was performed using bismuth(III) triflate, and highly functionalized 17-ketosteroids were obtained in good yields.⁹

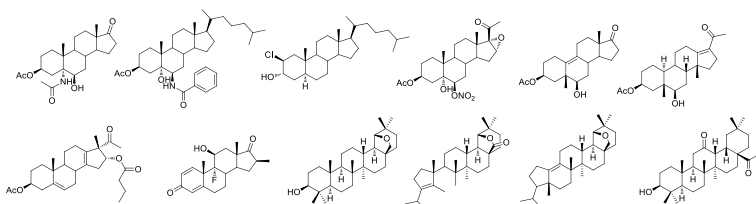


Figure 1: Examples of compounds obtained using the bismuth(III)-based new chemical processes developed in our research group.

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Study and Modulation of Inter-species Quorum Sensing by AI-2 Analogues

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Autoinducer-2 (AI-2) is a signalling molecule for bacterial inter-species communication. Examples of quorum sensing regulated behaviours are biofilm formation, virulence-factor expression, antibiotic production and bioluminescence. Ultimately, the understanding of the molecular mechanisms that bacteria use to regulate their behaviours can lead to the development of new therapies to control bacterial infections, and also to develop biotechnological applications for the control of industrial scale production of beneficial bacterial products, such as antibiotics or recombinant proteins.

A synthesis of (S)-4,5-dihydroxypentane-2,3-dione (DPD, **1**, Fig. 1), the precursor of AI-2, has been developed starting from methyl glycolate.¹ Using the same synthetic strategy and starting from methyl (S)- and (R)-lactates, four new analogues have been prepared and tested (Fig. 1). The new analogues had one more asymmetric center and the configuration of the new substituent exerted an important influence in its biological activity. Other analogues have been synthesised and tested for their quorum sensing activity, leading to useful structure/activity conclusions.

Studies towards the preparation of new DPD fluorescent markers, using different linkers, will also be presented. These new DPD probes are important tools to determine novel AI-2 receptors in important human pathogens such as *Pseudomonas aeruginosa*, and *Bacillus anthracis*. The discovery of new receptors involved in AI-2 signalling can lead to strategies to manipulate virulence in these pathogens and other closely related bacteria.

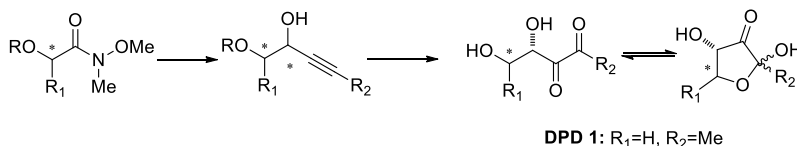


Figure 1: DPD and analogues synthesis.

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Development of a practical and efficient synthesis of an Active Pharmaceutical Ingredient

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Progression towards a scalable synthesis of an API, culminating in the first GMP manufacturing campaign, is described. Through process development, the discovery route was improved into an efficient industrial process. Hazardous reagents and solvents were substituted by more eco-friendly alternatives whilst improving the quality of the final API. Telescoping of the process reduced the total number of isolated intermediates. Also, crystallization development was of crucial importance to ensure product quality without the use of chromatographic steps.

Artificial and natural polymers: from synthesis and chemical modification to biomedical applications

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Living polymerization processes, in particular the Reversible Addition-Fragmentation chain Transfer (RAFT) polymerization, offer many benefits, which include the ability to control molecular weight and polydispersity, as well as to prepare block copolymers and other complex architecture polymers, difficult to obtain otherwise. By virtue of the RAFT mechanism, which relies in the introduction of a specific chain transfer agent (CTA) into the polymerization medium, polymers prepared by this technique are α,ω -functionalized. Moreover, RAFT polymerization is compatible with a great variety of monomers and reaction media.¹

Polysaccharides are promising materials for drug delivery systems due to their biocompatibility, degradation behavior, and nontoxic profile on administration. Recently, there has been a growing interest in the chemical modification of these polymers in order to create derivatives with tailored properties for specific purposes. In particular, regarding the development of appropriate vehicles for drug delivery, such modifications include the introduction of small functional groups.²

A few examples of synthesis of artificial polymers by RAFT and of chemical modification of polysaccharides will be presented, as well as their application in the development of systems for biosensing, imaging, and drug and gene delivery.³

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Synthesis and pharmacological evaluation of novel COMT inhibitors

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Catechol-O-methyltransferase (COMT) is a magnesium-dependent enzyme found in both the CNS and the periphery, which plays a key role in the inactivation of endogenous catechol neurotransmitters and xenobiotics. Inhibition of COMT provides therapeutic benefits in patients afflicted with Parkinson's disease (PD) undergoing treatment with the gold standard, levodopa. PD is a chronic neurological disorder associated with a reduction in striatal levels of the endogenous neurotransmitter dopamine. Levodopa is a biological precursor of dopamine, which is able to modulate cerebral levels of dopamine by penetrating into the brain. Clinical efficacy of the therapy can be dramatically improved by inhibiting the metabolic deactivation of levodopa in peripheral tissues. COMT inhibitors help to sustain the continuous delivery of dopamine to the striatum and thereby motor-related symptoms of PD are diminished.

A novel series of aryl- and heteroaryl-oxadiazolyl nitro-catechol derivatives of general structure **1** were prepared and evaluated for their COMT inhibitory ability in different animal species.¹ One compound from this series, namely opicapone (BIA 9-1067) exhibited potent, long-acting and peripheral inhibition of COMT.² Opicapone is currently under clinical phase III evaluation for the treatment of PD.^{3,4}

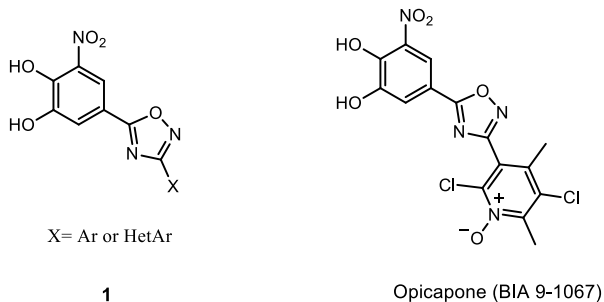


Figure 1: Novel aryl- and heteroaryl-oxadiazolyl nitro-catechol derivatives.

Chemical development and pharmacological evaluation of opicapone and its related analogues will be presented.

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Bioactivation of the anti-HIV drug abacavir to an electrophilic aldehyde: *in vitro* and *in vivo* approaches.

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The nucleoside reverse transcriptase inhibitor abacavir is associated with acute hypersensitivity reactions, often leading to drug discontinuation. Moreover, an association between long-term abacavir use and increased risk of myocardial infarction, though still controversial, has been reported. Bioactivation to a reactive aldehyde, capable of modifying self-proteins, is thought to be involved at the onset of these adverse reactions. We have proposed that a conjugated aldehyde is the electrophilic intermediate primarily responsible for reaction with the *N*-terminal valine of hemoglobin via Schiff base formation *in vitro*¹ and subsequently obtained evidence for this pathway in rats administered abacavir². More recently, we investigated abacavir bioactivation to aldehydes in humans by assessing the presence of abacavir adducts with the *N*-terminal valine of hemoglobin in HIV-infected patients on a standard anti-HIV regimen containing abacavir³. Following *N*-alkyl Edman degradation and HPLC-ESI-MS/MS analysis, the ABC-Valine Edman adduct was identified by comparison with a synthetic standard in 3/10 patients (50±16 years old; 560±280 CD4). These results represent the first report of abacavir metabolism to a conjugated aldehyde in humans. Moreover, by demonstrating that abacavir can be bioactivated to a metabolite subsisting long enough *in vivo* to undergo protein haptentation we are providing important clues to the possible role of this metabolic pathway at the onset of abacavir-induced toxic events. Therefore, the search for causal relationships between the formation of abacavir-derived protein adducts and the occurrence of abacavir-induced toxic events in human patients is worth pursuing in further toxicological studies with larger cohorts.

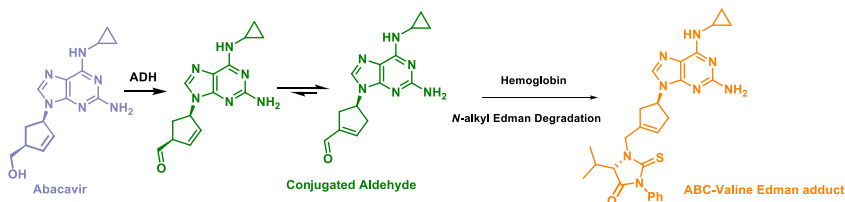


Figure 1: Alcohol dehydrogenase (ADH) mediated bioactivation pathway of the anti HIV drug abacavir to the electrophilic conjugated aldehyde and its haptentation mechanism.

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Ten Years of Catalytic "Asymmetric" Activity at CQE-UE: The First Decade

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Catalytic asymmetric synthesis stands out as the most efficient and elegant means of accessing enantiomerically pure compounds. Considering the fact that about 80% of all the pharmaceuticals on the market are chiral, this strategy is therefore a highly useful technology for the pharmaceutical industry. Our mission over the last 10 years has been the development of novel catalytic systems of use to the pharmaceutical industry. The development of these catalytic systems (Figure 1), their application, including their immobilization to solid supports will be discussed in this communication.¹⁻³

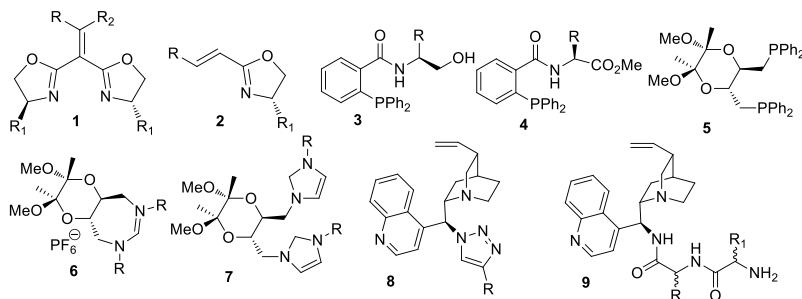


Figure 1: Some of the chiral ligands and organocatalysts developed to date in our lab.

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