# New synthetic methodologies and syntheses of biologically active molecules


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Our research activities focus on the synthesis of biologically active compounds for the various stages of drug development. Several of our projects address the development of basic synthetic methodology, with special emphasis on asymmetric synthesis. Others are devoted to the synthesis of compounds of known therapeutic interest, for which the emphasis is placed on the reliability, efficiency and scalability of the processes. Finally, other projects concern drug discovery and aim to prepare chemical libraries for biological screening.

**Asymmetric catalysis. Basic synthetic methodologies**

***New strategies in the Pauson-Khand reaction***

The Pauson-Khand reaction (PKR) is one of the most powerful reactions for the preparation of cyclopentanic compounds. The PKR is a cobalt-promoted or catalysed cycloaddition between an alkene and an alkyne with insertion of a carbon monoxide molecule to give a cyclopentenone. We use these cyclopentenones as starting materials for the synthesis of biologically active substances.

A ligand-based asymmetric version of the PKR must include a diastereoselective coordination step of the ligand with the cobalt carbonyl complex of the alkyne. Over the last year, we have studied how non-bonding interactions enhance the selectivity of this coordination. Finding the key for a high selectivity would open the door to development of a practical asymmetric version of the PKR.

With our hemi-labile P,S-ligands (CamPHOS and PuPHOS), we have disclosed how a non-classical hydrogen bond contact within the ligand and the dicobalt carbonyl substrate can dramatically increase selectivity (Solà *et al*, 2005; Solà *et al*, 2006). Although these results are significant due to the novelty of our approach, the use of the resulting diastereomerically pure complexes in the intermolecular PKR suffer several drawbacks. (See Figure 1.)

***A new family of ligands for metal-catalysed reactions***

To overcome the problems associated with the aforementioned approach, we designed a second generation of hemi-labile P,S-ligands. We synthesised these unprecedented, chiral non-racemic *N*-phosphinosulfinamides, and found that these ligands bound to dicobalthexacarbonyl complexes with high selectivity. The resulting complexes were successfully applied to the asymmetric PKR. The importance of these results led us to file a patent (Spanish application EP2006-02665) for these compounds and their use in PKR, before publishing the results. (See Figure 2.)

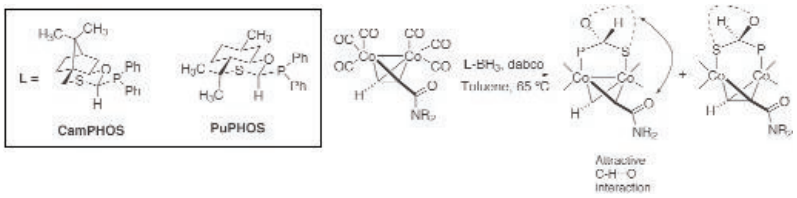


***Figure 1**. Diastereoselective coordination of P,S-ligands directed by a non-classical hydrogen bond.*

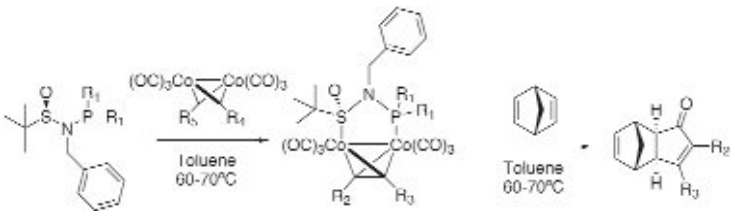


***Figure 2**. New N-phosphinosulfinamide ligand and their use in enantioselective Pauson-Khand reactions.*

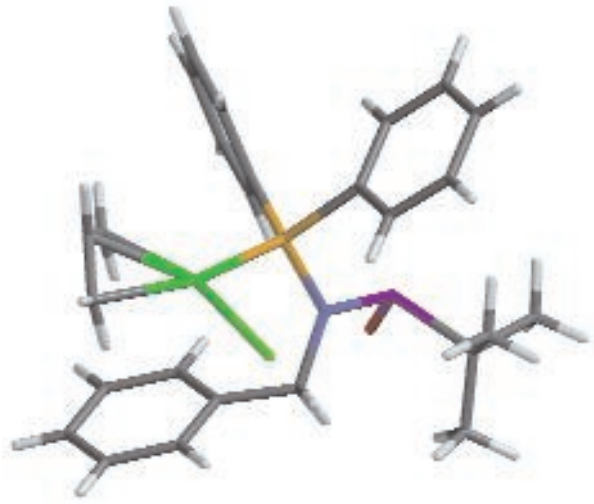

***Figure 3**. X-ray diffraction of a palladium complex of our N-phosphinosulfinamide ligand.*

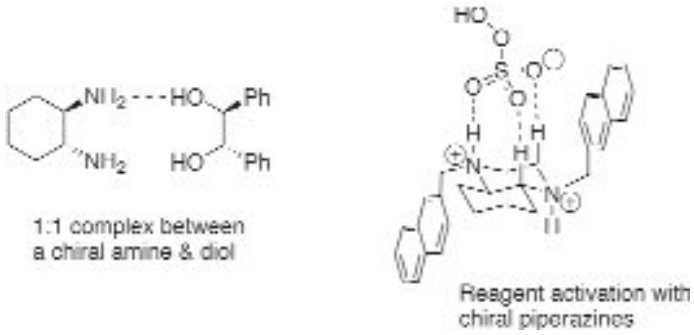


***Figure 4**. Complexes stabilized by hydrogen-bond interactions. An approach to new organocatalytic methods.*

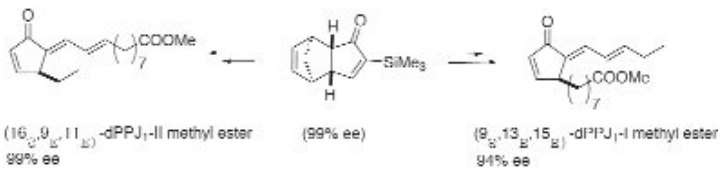


***Figure 5**. Syntheses of dehydrophytoprostanes from an intermolecular Pauson-Khand adduct.*

Application of the new *N*-phosphinosulfinamide ligands to other metal-catalysed processes is now being studied in our labs. The chemical nature of these ligands makes several coordination modes possible for a determined metal centre. Thus, they can act as monodentate ligands through phosphorous, or alternatively, as bidentate ligands through either phosphorous-oxygen or phosphorous-sulfur. To date, we have determined the structure of a palladium complex in which the ligand acts as a monodentate ligand. Interestingly, even in this case, these ligands provide a highly asymmetric environment around the metal centre. (See Figure 3.)

### *Assemblies of small molecules in asymmetric catalysis*

We are currently studying catalytic reactions that do not use metal catalysts – also known as organocatalysis – with the aim of developing useful and clean asymmetric methodologies. One of our approaches is to form 1:1 complexes of organic molecules that could work in tandem as a catalyst. It is known that 1,2-diamines and 1,2-diols form 1:1 complexes in solution and in solid state. We are now exploring whether these 1:1 complexes can work as catalysts in the asymmetric Diels-Alder reaction via hydrogen bond activation of the substrates. We are also exploring the activation of these reagents through their complexing to chiral molecules via non-bonding interactions. In particular, we are studying the complex formation capacity of chiral piperazines and their corresponding salts. The ultimate goal is to activate oxidising agents such as oxone (sodium peroxomonosulfate), and to use these complexes in the asymmetric oxidation of pro-chiral substrates. (See Figure 4.)

## Synthesis of biologically active compounds

### *Synthesis of five-membered ring compounds*

As mentioned above, one of the best ways to prepare five-membered ring compounds is by the PKR. Prostaglandins are among the most important cyclopentanic compounds since they exhibit a wide variety of functions and biological activities. Some recently developed drugs are synthetic analogues of prostaglandins. Phytoprostanes are not as well-known. However, in the last few years, interest in their biological activity has increased considerably. These compounds have in common a cyclopentenone or a hydroxycyclopentenone ring, making them suitable substrates for synthesis by Pauson-Khand chemistry. In collaboration with Prof P Evans (Trinity College, Dublin), we have transformed the Pauson-Khand adduct of trimethylsilylethyne and norbornadiene into several dehydroisoprostanes (dPPJ1; see Figure 5). We are currently working on the transformation of Pauson-Khand adducts into prostaglandines

and phytoprostanes. We have also prepared a chemical library that has been tested in the search for specific inhibitors of beta-catenin.

***Enantioselective synthesis of amino acids and amino alcohols***

Amino alcohol fragments are present in many natural compounds such as aza-sugars, amino sugars, amino acids or sphingosines. We are currently working on the enantioselective synthesis of all these families of compounds, by developing convergent approaches based on the regioselective opening of epoxides, or sulfates, prepared by Sharpless asymmetric epoxidation (SAE) or dihydroxylations (AD).

We have recently published a methodology for the preparation of α-hydroxy-β-amino acids (Alonso *et al*, 2005), which has been applied to a practical, scalable synthesis of (2R, 3R)-2-amino-3-hydroxy-3-cyclohexylpropanoic acid, a key component of the anti-inflammatory and HIV antagonist drug ONO-4128 (Alonso *et al*, 2005; see Figure 6.)

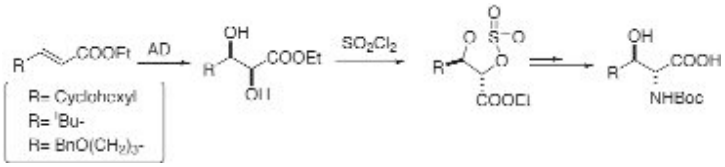


***Figure 6**. Enantioselective synthesis of β-hydroxy-α-amino acids.*

One of our most useful approaches for the preparation of cyclic compounds is based on the use of unsaturated epoxides to take advantage of the ring-closing metathesis (RCM) reaction. This year we have described the enantioselective preparation of all stereoisomers of 6-amino-cyclohex-3-ene-1,2-diols (4-deoxy-3-conduramines), key building blocks for the syntheses of a large range of natural products. Moreover, diastereoselective dihydroxylation of the compounds provided a new family of aminocyclitols (deoxyinosamines; Alegret *et al*, 2006). These compounds have been tested as potential β-catenin inhibitors, as explained below. (See Figure 7.)

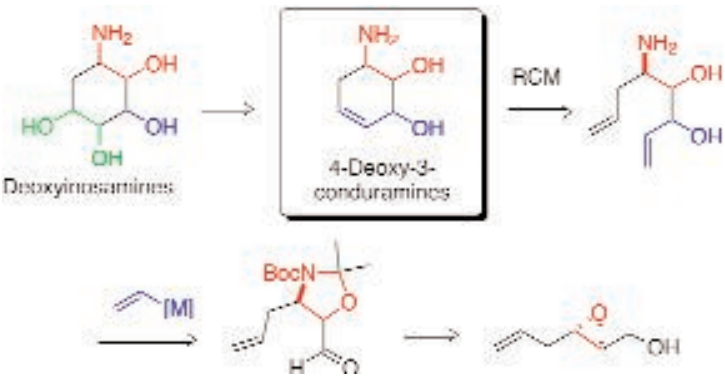


***Figure 7**. Synthetic approach to deoxyconduramines and aminocyclitols.*

**Synthesis of new chemical libraries for drug-discovery**

***Synthesis of specific inhibitors of β-catenin***

This project is being developed in collaboration with Prof Mireia Duñach (UAB) and Prof Antonio Garcia de Herreros (UPF).

The progressive accumulation of nuclear β-catenin that deregulates cellular proliferation, differentiation, and migration has been described as an initial event for the development of colonic tumourigenesis. In addition to its structural role in epithelial junctions, β-catenin activates TCF-4-mediated transcription of genes required for cell proliferation. (See Figure 8.)

Our hypothesis is that tumour progression can be arrested by blocking the aberrant transcription mediated by β-catenin. Our main goal is to identify of small molecules that specifically block β-catenin-

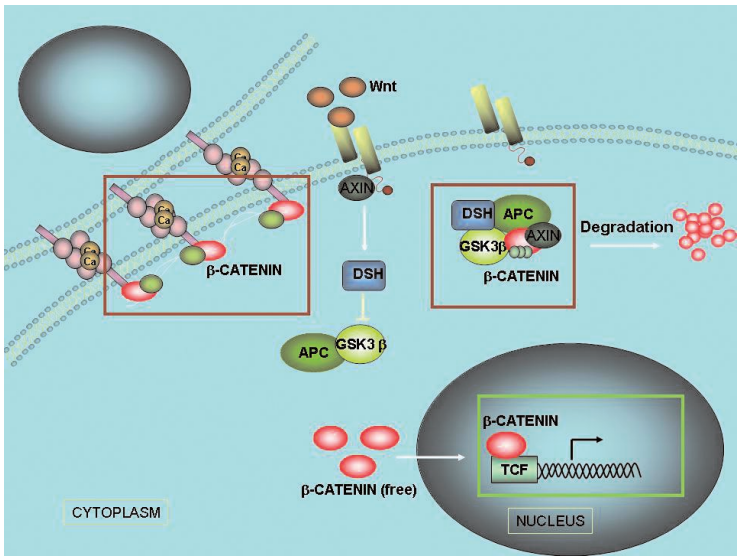


***Figure 8**. Double role of β-catenin: as a regulator of adherent junctions and as a transcriptional co-activator of genes involved in tumorigenesis.*

mediated transcription, which is essential for tumour development. These molecules could therefore be potentially active in colon tumour treatment.

We are searching for small molecules that do not alter the interaction of β-catenin with: a) factors involved in the establishment of adherens junctions (E-cadherin, α-catenin) and b) factors involved in the degradation complex (APC, axin). To this end, we have prepared several chemical libraries that have been screened in Duñach and Garcia de Herreros laboratories. We have tested a library based on the PKR, a library of amino alcohols, several non-natural amino acids derivatives and a peptidic library. The results are promising, although the work is still not ready for publication.

***Synthesis of Somatostatin analogues***

This year we have started a new project in collaboration with BCN-Peptides. A leader in API peptides, this company was recently awarded a CIDEM grant for this project. We have prepared and provided them with several adequately protected mesityl amino acids, which have been used in the synthesis of ten peptidic Somatostatin analogues. The biological activity of these new compounds is now being tested.

**PUBLICATIONS**

Alegret C, Benet-Buchholz J and Riera A (2006) Stereodivergent syntheses of conduramines and aminocyclitols. Organic Letters, 8:3069-3072

Alonso M, Santacana F, Rafecas L and Riera A (2005) Practical, scalable, enantioselective synthesis of (2R,3R)-N-Boc-2-amino-3- cyclohexyl-3-hydroxypropanoic acid. Organic Process Research & Development, 9:690-693

Alonso M and Riera A (2005) Improved preparation of beta-hydroxy-alfa-amino acids: direct formation of sulfates by sulfuryl chloride. Tetrahedron: Asymmetry, 16:3908-3912

Cabot R, Lledó A, Revés M, Riera A, Verdaguer X (2007) Kinetic studies on the cobalt-catalysed norbornadiene intermolecular Pauson-Khand reaction. Organometallics, 26:1134-1142

Islas-Gonzalez G, Benet-Buchholz J, Maestro MA, Riera A and Pericas MA (2006) Boron trifluoride-induced, new wtereospecific rearrangements of chiral epoxy ethers. Ready access to enantiopure 4-(diarylmethyl)-1,3-dioxolanes and 4,5-disubstituted tetrahydro-benzo[c]oxepin-4-ols.J Org Chem, 71:1537-1544

Solà J, Riera A, Verdaguer X and Maestro MA (2005) Phosphine-substrate recognition through the C-H...O hydrogen bond: Application to the asymmetric Pauson-Khand reaction. J Am Chem Soc, 127:13629-13633

Solà J, Riera A, Verdaguer X and Maestro MA (2006) C-H···O hydrogen bond-directed ligand exchange reaction: Diasteroselective synthesis of P,S-bridged (μ-alkyne)Co2(CO)4 complexes. Organometallics, 25:5795-5799

**RESEARCH NETWORKS AND GRANTS**

*Vers una nova família de catalitzadors per a processos reductius i síntesi asimètrica*
Distinció de la Generalitat de Catalunya per a la promoció de la recerca Universitària. Categoria joves investigadors
DURSI (Generalitat de Catalunya): 2002-2006
Principal investigator: Xavier Verdaguer i Espaulella

*Identificación de inhibidores específicos de la actividad transcripcional de la beta-catenina en cáncer de colon*
Investigación biomédica, Convocatoria oncología, BM 05-68-0
Fundació La Caixa: 2006-2008
Project coordinator: Mireia Duñach Masjuan
Principal investigator of subproject: Antoni Riera Escale

*Síntesis enantioselectiva de moléculas bioactivas mediante catálisis asimétrica: Reacciones de Pauson-Khand, organocatálisis y oxidaciones de Sharpless*
Programme: NCTQ - Programa Nacional de ciencias y tecnologías químicas, CTQ2005-00623/BQU
DIGI - Dirección General de Investigación: 2006-2008
Entidades participantes: SPCT - Secretaría de estado de política científica y tecnológica / MEDU - Ministerio de Educación y Ciencia
Principal Investigator: Antoni Riera Escale

*Identificació d'inhibidors específics de l'activitat transcripcional de la beta-catenina en la progressió tumoral*
Ajuts econòmics a projectes de recerca sobre càncer, 050630/31/32
Fundació La Marató de TV3: 2006-2008
Project coordinator: Mireia Duñach Masjuan
Principal investigator of subproject: Antoni Riera Escale

**OTHER FUNDING SOURCES**

Three contract research projects with Enantia SL through the Fundació Bosch i Gimpera. Project numbers: FBG304021; FBG303967 and FBG303414

**COLLABORATIONS**

*Synthesis of specific inhibitors of beta-catenin*
Mireia Duñach (Universitat Autònoma de Barcelona, Spain)

*Synthesis of specific inhibitors of beta-catenin*
Antonio Garcia de Herreros (Universitat Pompeu Fabra, Spain)

*Asymmetric catalysis*
Miquel A Pericàs (The Institute of Chemical Research of Catalonia, Spain)

*Synthesis and biological activity of phytoprostanes*
Paul Evans (Trinity College, University of Dublin, Ireland)

*Synthesis and biological activity of phytoprostanes*
Martin Müller (Julius-von-Sachs-Institut of Biosciences, Universität Würzburg, Germany)

*Synthesis of pharmaceutically active compounds*
Enantia SL, Spain
Llorenç Rafecas, Alex Comely, Nicolas Tesson

*Synthesis of Somatostatin analogues*
BCN Peptides SL, Spain
Berta Ponsati, Jimena Fernández-Carneado, Marc Gomez

*Antoni Riera Escalé's group, March 2006.*