



Syntheses of biologically active molecules and development of new synthetic methodologies

Our group focuses on synthesising biologically active compounds for the various stages of drug development. Several of our projects are devoted to the development of basic synthetic methodology, with a special emphasis on asymmetric synthesis, while others address the synthesis of compounds of known therapeutic interest, in which emphasis is placed on the reliability, efficiency and scalability of the processes. Finally, other projects underway are related to drug discovery; these aim to prepare new compounds for biological screening.

Catalytic and asymmetric reactions. Basic synthetic methodologies

New ligands for metal-catalysed reactions

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. To date, the best approach to attain an asymmetric version of the PKr is to use chiral ligands. Some years ago, we designed a second generation of hemi-labile P,S-ligands with an unprecedented structure showing a backbone constituted by four linked heteroatoms (P-N-S-O; Figure 1). We successfully synthesised these chiral non-racemic *N*-diphenylphosphino *tert*-butylsulfonamides and found that they bound to dicobalthexacarbonyl complexes with high selectivity. The resulting complexes gave excellent yields and high enantiomeric excesses (up to 99% ee) in the intermolecular PKr (Solà *et al.*, 2007).

In 2009 we have explored the scope of these highly modular P,S ligands. Firstly, we have tested the effect of the substituent at sulfur (R^1). A family of PNSO ligands with electron-deficient sulfinyl groups has been synthesised. Reaction with Co_2 -alkyne complexes yields P,S-bridged complexes. These complexes have been used to study the metal-bonding of the distinct sulfinyl groups. Infrared spectroscopy (IR), X-ray and Pauson-Khand reactivity studies indicated that electron-deficient sulfinyl groups provide enhanced sulfur-metal bonding. Among the sulfinyl groups studied the trifluoromethyl PNSO ligand afforded the strongest S-Co bond. We have therefore established that the electron-deficient substituents linked to the sulphur atom of the ligand favour backbonding with the metal. Consequently, the resulting cobalt complexes are less hemilabile (Revés *et al.*, 2009).

Furthermore, we considered that the replacement of the nitrogen atom by a carbon atom would increase the stability of both

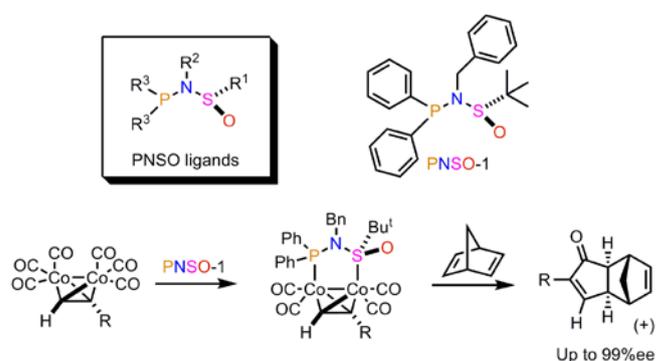


Figure 1. Asymmetric Pauson-Khand reaction using PNSO ligands.

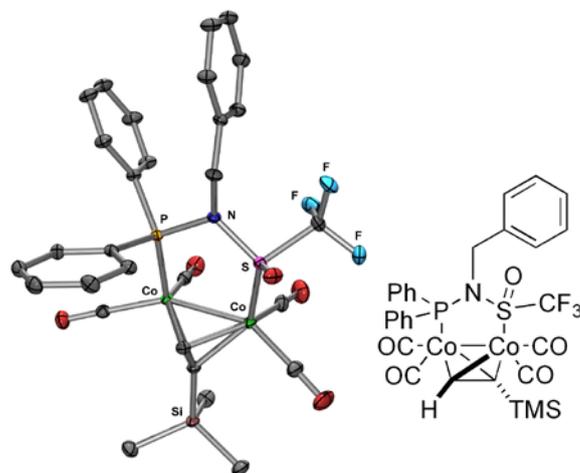


Figure 2. X-ray structure of a cobalt carbonyl complex coordinated to a trifluoromethyl PNSO ligand.

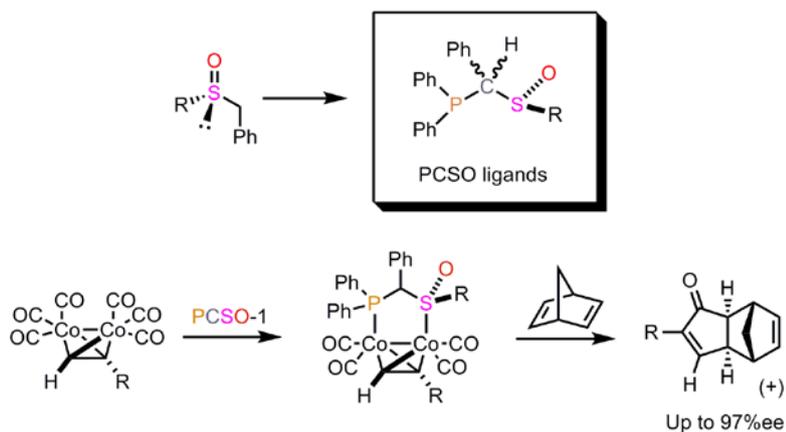


Figure 3. Asymmetric Pauson-Khand reactions with PCSO ligands.

ligands and the corresponding metal complexes. Ligands with a central carbon atom (PCSO) have been prepared by phosphinylation of benzyl and homobenzyl sulfoxides. Therefore, a new family of enantiomerically pure *p*-tolyl and *tert*-butyl sulfinylmethylphosphine ligands (PCSO ligands) with an extra chiral centre at the carbon atom have been described. Ligand exchange reaction of these compounds with Co₂-alkyne complexes afforded up to 6:1 dr. The resulting bridged complexes were tested in the intermolecular PKr to provide up to 97% ee (Ferrer *et al*, 2009).

Research Group Members

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Although initially designed for PKr, PNSO ligands have the capacity to bind to other metals and, a priori, can be useful in other types of metal organometallic asymmetric reactions. We have studied this possibility thoroughly and have pursued the formation of new organometallic complexes. We have prepared and characterised the rhodium (I) complexes of *N*-phosphino-*tert*-

butylsulfonamide ligands that are potentially useful in asymmetric hydrogenation. In this case PNSO ligands work either as P,O or P,S chelating ligands when attached to the square planar rhodium centre. Complexes bearing diene ligands, such as [Rh(PNSO)(NBD)][TfO] and [Rh(PNSO)(COD)][TfO], provided P,O coordination, while [Rh(PNSO)₂][TfO]-type complexes provided P,S coordination. Ligand exchange experiments with mono and bidentate phosphines afforded evidence of the hemilabile behaviour of the PNSO ligands (Achard *et al.*, 2009).

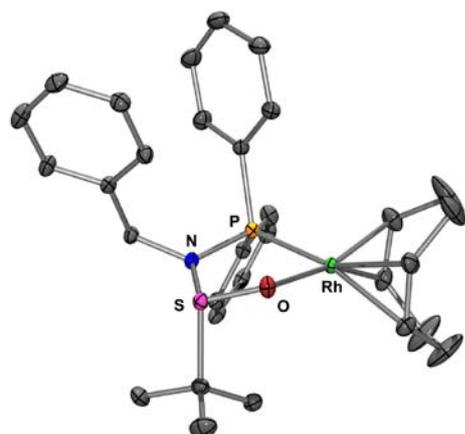


Figure 4. X-ray structure of a rhodium complex with a P,O coordination to a PNSO ligand.



Figure 5. Asymmetric PKr of symmetrically substituted alkynes.

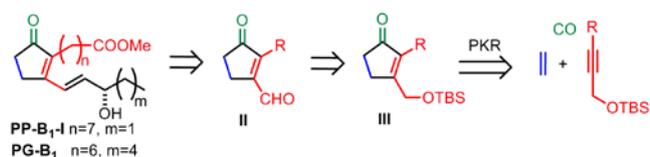


Figure 6. Retrosynthetic scheme of our synthesis of prostaglandin and phytprostane B₁.

New developments in the PKr

Prior to our work, no asymmetric PKr with symmetrically substituted alkynes had been developed. These acetylenes have the advantage that when coordinated to a bidentate ligand they can give rise to only one diastereomer, thereby preventing the diastereomeric separation of the complexes. However, the asymmetric version is especially difficult because the olefin insertion must select between the two almost identical C-Co bonds. We discovered that PNSO ligands can be efficiently used in this process. The chirality of the cobalt S-bonded sulfinyl moiety was found to direct olefin insertion into one of the two possible cobalt-carbon bonds in the alkyne complex. Therefore, we developed the first asymmetric PKr with symmetrically substituted alkynes (Ji *et al.*, 2009).

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 through the PKr. Prostaglandins are among the most relevant cyclopentanic compounds because they exhibit a wide variety of functions and biological activities. We have described a new approach to synthesise prostaglandin and phytprostanes B₁. The key step in this strategy is an intermolecular PKr between a silyl-protected propargyl acetylene and ethylene. This reaction, promoted by NMO in the presence of 4Å molecular sieves, afforded the 3-*tert*-butyldimethylsilyloxymethyl-2-substituted-cyclopent-2-en-1-ones (III) in good yield and with complete regioselectivity. Deprotection of the silyl ether, followed by Swern oxidation, gave 3-formyl-2-substituted-cyclopent-2-en-1-ones (II). Julia olefination of the aldehydes II with the suitable chiral sulfone allowed preparation of PPB1 type I and PG-B₁ (Vázquez-Romero *et al.*, 2009).

Enantioselective synthesis of amino acids and peptides

We have prepared several new non-natural amino acids and used them in the preparation of Somatostatin analogues. The biological activity of these new compounds revealed that they are as active as the natural hormone in some receptors but much more selective. We are now studying their structure by NMR, in collaboration with Maria Macias (IRB Barcelona). We aim to correlate the biological activity with the structure in order to design analogues with an improved selectivity profile and higher stability in plasma.

Scientific output

Publications

Achard T, Benet-Buchholz J, Riera A and Verdaguer X. Cationic rhodium (I) complexes of N-phosphino-tert-butylsulfonamide ligands: Synthesis, structure and coordination modes. *Organometallics*, **28**, 480-87 (2009)

Ferrer C, Riera A and Verdaguer X. Sulfinylmethyl phosphines as chiral ligands in the intermolecular Pauson-Khand reaction. *Organometallics*, **28**, 4571-76 (2009)

Ji Y, Riera A and Verdaguer X. Asymmetric intermolecular Pauson-Khand reaction of symmetrically substituted alkynes. *Org Lett*, **11**(19), 4346-49 (2009)

Reves M, Riera A and Verdaguer X. PNSO ligands as a tool to study metal bonding of electron-deficient sulfinyl groups. *Eur J Inorg Chem*, **29**, 4446-53 (2009)

Riera A. Asymmetric synthesis of nitrogen heterocycles. *Angew Chem Int Ed*, **48**, 9590 (2009)

Vázquez-Romero A, Cárdenas L, Blasi E, Verdaguer X and Riera A. Synthesis of prostaglandin and phytoprostane B1 via regioselective intermolecular Pauson-Khand reactions. *Org Lett*, **11**(14), 3104-07 (2009)

Research networks and grants

Nous catalizadors quirals amb lligands de tipus fosfinosulfonamida per a síntesi asimètrica
Enantia SL (2009)

Principal investigator: Antoni Riera

Síntesis enantioselectiva de compuestos biológicamente activos y desarrollo de nueva metodología sintética
Spanish Ministry of Science and Innovation, CTQ2008-00763 (2009-2011)

Principal investigator: Antoni Riera

Collaborations

Molecular orbital calculations
Santiago Olivella, CSIC (Barcelona, Spain)

Structural NMR studies of peptides
Maria Macias, IRB Barcelona (Barcelona, Spain)

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

Synthesis of cucurbituril derivatives
Miquel Pons, IRB Barcelona (Barcelona, Spain)

Synthesis of PPAR- γ inhibitors

Annabel Fernández Valledor, University of Barcelona (Barcelona, Spain)

Synthesis of specific inhibitors of β -catenin

Mireia Duñach, Autonomous University of Barcelona (Barcelona, Spain)