Vidal Research Group

Group Leader: Anton Vidal
Group Scientific Coordinator: Héctor Fernández
Postdoctoral Researchers: José Luis Núñez / Mónica Vaquero
PhD Students: Ignacio Mon (until Oct.) / Balakrishna Bugga / Joan Ramon Lao / Carlos Manuel León (until Sept.) / Laura Rovira / Lucas Carreras
Administrative Support: Paula Segovia

Abstract

Our past and current objectives encompass the ***design and development of efficient catalytic enantioselective methodologies*** and their application to the preparation of targets of biological, pharmacological and agrochemical relevance. Designing modular catalysts and versatile synthetic procedures for their preparation, and performing computational analyses of the catalytic event, are key elements in our strategy.

Two main objectives are pursued within the group: In the first instance, we aim to develop, highly modular enantiopure *P*–*OP* ligands for asymmetric organometallic catalytic synthesis. Secondly, we aim to devise strategies to generate a set of supramolecular chiral ligands which resemble a privileged structure yet at the same time offer a range of closely related geometrically active sites.

Our group has developed extensive methods for two-step synthesis of highly modular 1,2-*P*–*OP* ligands (see Figure 1): *ring opening of enantiopure epoxides* with phosphorus nucleophiles (*RSC Adv.* (**2014**), 58440-58447), which enables incorporation of phosphino groups that contain sterically and electronically diverse substituents (PR^5_2 group); and *O-phosphorylation* of the 1,2-*P*–*OH* derivatives, to introduce an array of structurally diverse phosphite groups into the ligands (OPR^6_2 moiety). We have also described efficient strategies for 1,1-*P*–*OP* ligands (Scheme 1).

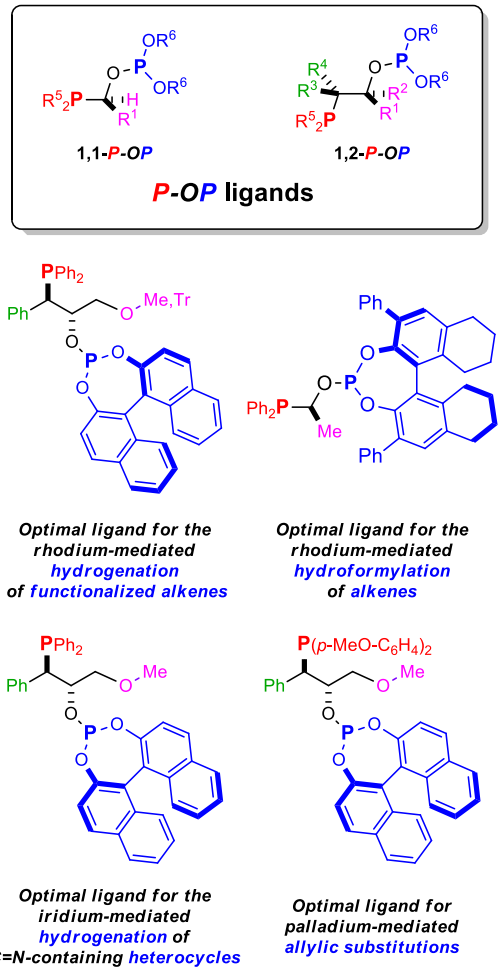

Fig. 1 – Lead *P*–*OP* ligands in the studied enantioselective transformations

We have tuned performance of the catalysts derived from the aforementioned *P*–*OP* ligands *via* modification of the characteristic parameters of the different modules (*i.e.* the electronic and steric properties of the different molecular fragments), following the principles of molecular interactions and/or computational studies. This sound approach has led to the development of highly efficient catalysts for rhodium-mediated hydrogenation of functionalized alkenes, iridium-mediated hydrogenation of C=N-containing heterocycles (*Green Chem.* (**2014**), *3*, 1153-1157), rhodium-mediated hydroformylation of alkenes (*Organometallics* (**2014**), *12*, 2960-2963 and *Chem. Eur J.* (**2014**), *20*, 15375-15784) and palladium mediated allylic substitutions.

Unprotected indoles have been efficiently converted to enantiomerically enriched indolines (up to 91% ee) by a stepwise process: (Reusable) Brønsted acid-mediated C=C isomerization and asymmetric hydrogenation using enantioselective iridium catalysts derived from *P*–*OP* ligands (*Green Chem.* (**2014**), *3*, 1153-1157; see Figure 2). This straightforward combination of reusable Brønsted acids, which activate the indole ring for hydrogenation by breaking its aromaticity, and enantiomerically pure $[Ir(P–OP)]^+$ complexes as hydrogenation catalysts affords the resulting indolines with high enantioselectivities

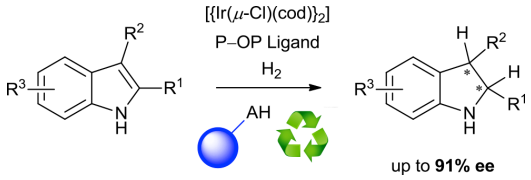

Fig. 2 – $[Ir(P–OP)]$-mediated asymmetric hydrogenation of indoles

The group has prepared of a set of narrow bite-angle *P*–*OP* ligands. The first type of ligands contain a stereogenic phosphine group (*Organometallics* (**2014**), *12*, 2960-2963), whilst the second one contains a stereogenic carbon between the phosphine and phosphite groups (*Chem. Eur J.* (**2014**), *20*, 15375-15784). The synthesis of the latter was based on a CBS-catalyzed asymmetric reduction of phosphomides. The structure of the resulting 1,1- *P*–*OP* ligands, which was selectively tuned through adequate combination of the configuration of the stereogenic carbon, its substituent and the phosphite fragment, proved crucial for providing a rigid environment around the metal center, as evidenced by X-ray crystallography. These new ligands enabled very good catalytic properties in the Rh-mediated enantioselective hydrogenation and hydroformylation of challenging and model substrates (up to 99% ee; see Figure 3). Whereas for asymmetric hydrogenation the optimal *P*–*OP* ligand depended on the substrate, for hydroformylation, a single ligand was the highest-performing one for almost all studied substrates: it contains an (*R*)-configured

stereogenic carbon between the two phosphorus ligating groups, and an (*S*)-configured 3,3'-diphenyl-substituted biaryl unit.

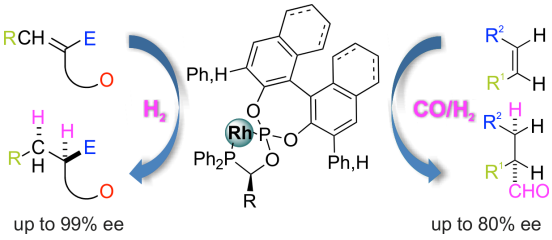

Fig. 3 – Catalysts derived from the lead 1,1-*P*–*OP* ligand for asymmetric hydroformylations and hydrogenations

Our group has devised a strategy for generating a set of supramolecular ligands that resemble a privileged structure and offer the possibility of creating various geometrically close active sites. The main advantage of this approach is that the geometry of the catalytic site can be modified through reversible supramolecular interactions. In these ligands, the two phosphorus ligating groups are separated by a polyether spacer that serves as the "regulation" site of catalytic activity. Complexation of the *regulating agent* to the polyether chain brings the two phosphorus ligating groups close together (this is the *template effect* promoted by the RA), thus facilitating the formation of a chelate in the presence of the corresponding metal precursor for hydroformylations or hydrogenations. Furthermore, the RA also induces the catalytic site to adopt a particular geometry, depending on its size and shape (this is the *regulation effect* on the supramolecular complex to be used as an enantioselective catalyst).

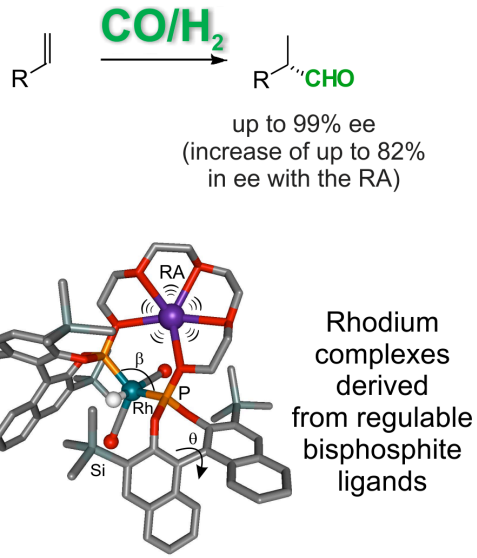

Fig. 4 – Lead supramolecularly regulated catalyst for asymmetric hydroformylations

In response to ICIQ's aspiration of fostering collaborative research projects with industrial partners, we have also directed our efforts in the field of catalysis for industrial targets. This collaboration, which is ongoing, involves the development of sustainable processes for the preparation of isocyanate precursors (WO2014187756A1 (**2014**)).

Articles and Patents

"Asymmetric Hydrogenation of Unprotected Indoles Using Iridium Complexes derived from P-OP Ligands and (Reusable) Brønsted Acids"
Green Chem. (**2014**), *3*, 1153-1157
J. L. Núñez-Rico, H. Fernández-Pérez, A. Vidal-Ferran

"Supramolecular Catalysis. Part 1: Non-covalent Interactions as a Tool for Building and Modifying Homogeneous Catalysts"
Chem. Soc. Rev. (**2014**), 1660-1733
M. Raynal, P. Ballester, A. Vidal-Ferran, P. W. N. M. van Leeuwen

"Supramolecular Catalysis. Part 2: Artificial Enzyme Mimics"
Chem. Soc. Rev. (**2014**), 1734-1787
M. Raynal, P. Ballester, A. Vidal-Ferran, P. W. N. M. van Leeuwen

"MaxPHOS Ligand: PH/NH Tautomerism and Rhodium-Catalyzed Asymmetric Hydrogenations"
Adv. Synth. Catal. (**2014**), 795-804
E. Cristóbal-Lecina, P. Etayo, S. Doran, M. Revés, P. Martín-Gago, A. Grabulosa, A. R. Costantino, A. Vidal-Ferran, A. Riera, X. Verdaguer

"1,1-P–OP Ligands with P-Stereogenic Phosphino Groups in Asymmetric Hydrogenations and Hydroformylations"
Organometallics (**2014**), *12*, 2960-2963
J. R. Lao, J. Benet-Buchholz, A. Vidal-Ferran

“Enantiopure Narrow Bite-Angle P-OP Ligands: Synthesis, and Catalytic Performance in Asymmetric Hydroformylations and Hydrogenations”
Chem. Eur J. (**2014**), *20*, 15375-15784
H. Fernández-Pérez, J. Benet-Buchholz, A. Vidal-Ferran

“Ring-opening of Enantiomerically Pure Oxa-containing Heterocycles with Phosphorus Nucleophiles”
RSC Adv. (**2014**), 58440-58447
H. Fernández-Pérez, P. Etayo, J. L. Núñez-Rico, B. Bugga, A. Vidal-Ferran

“Preparation of zinc benzoato complex cluster compounds as catalysts in the reaction of amines with dialkyl carbonates”
WO2014187756A1 (**2014**).
T. Dreier, S. Wershofen, A. Vidal-Ferran, R. Haak