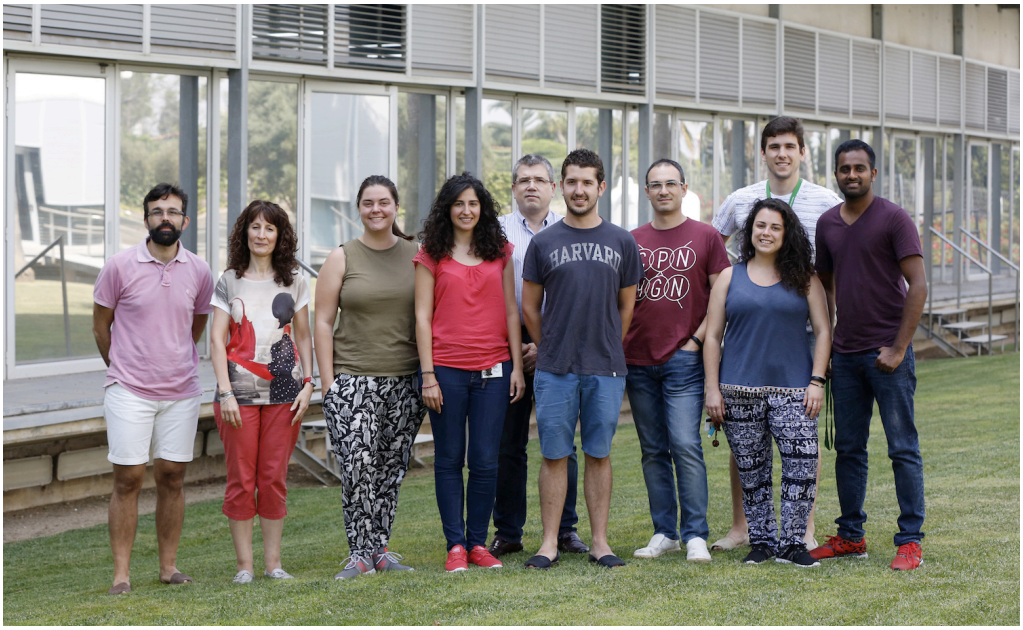
Vidal Research Group



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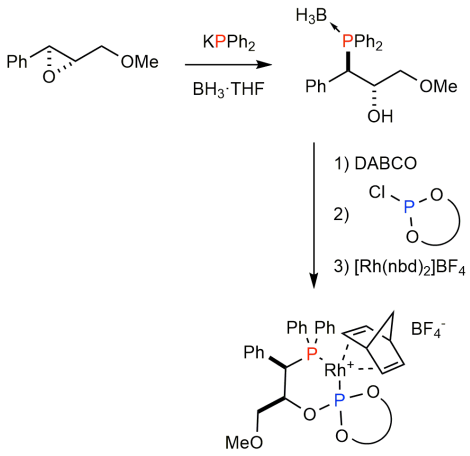
Abstract

Our past and current objectives encompass the ***Design of Efficient Enantioselective Catalysts for Transformations of Interest***, and the study of their use to prepare enantiomerically pure products of biological, pharmaceutical or agrochemical interest. Crucial aspects of this work include modular design of the catalysts; use of versatile synthetic procedures (organic and inorganic transformations, or supramolecular processes); incorporation of regulation mechanisms for their active-site geometry; and computational study of their catalytic cycles (through collaborations).

We have two ongoing objectives: firstly, to develop new privileged structures in asymmetric catalysis (*P*–*OP* Ligands), using versatile covalent chemistry; and secondly, to generate a set of supramolecular catalysts that resemble a privileged structure and include the possibility of offering a range of closely related catalytic sites.

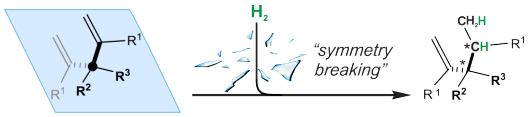
Our research group is involved in the design and synthesis of highly modular enantiopure phosphine-phosphite (*P*–*OP*) ligands for *a priori* use in various asymmetric transformations.
We have described a practical and chromatography-free method of preparing enantiopure rhodium(I) complexes that can be used as efficient catalysts for the asymmetric hydrogenation of functionalized alkenes, the hydrogenative kinetic resolution of vinyl sulfoxides and the desymmetrization of achiral dienes (*Synthesis* (**2016**), *48*, 997-1001; see Figure 1). The synthetic route starts with the ring-opening of an enantiopure Sharpless epoxy ether with a phosphorus nucleophile followed by isolation of the borane-protected phosphino alcohol derivative by crystallization. The subsequent cleavage of this borane complex, the *O*-phosphorylation of the resulting phosphino alcohol with the corresponding phosphorus electrophiles (chlorophosphite derivatives), and finally the complexation of the *in situ* generated *P*–*OP* ligands with $[Rh(nbd)_2]BF_4$, followed by crystallization, rendered the target pre-catalysts in multi-gram amounts. Our described synthetic protocols may enable these efficient hydrogenation catalysts to be easily accessed by the "asymmetric catalytic community".



Practical two-step synthesis of rhodium hydrogenation pre-catalysts
(gram amounts, free of chromatography)

Fig. 1 – Practical synthesis of Rh-*P*–*OP* pre-catalysts for hydrogenative transformations

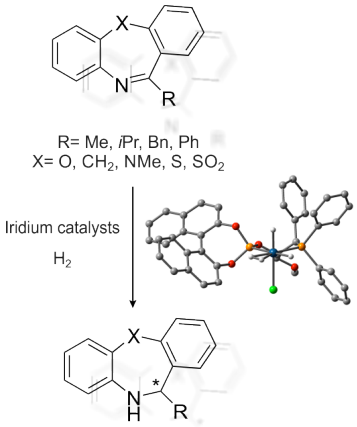
We became interested in developing enantioselective catalysts derived from *P*–*OP* ligands for challenging transformations, for which no satisfactory solutions in terms of efficiency, chemo- and stereo-selectivity had been developed. In this way, highly efficient catalytic stereoselective hydrogenative desymmetrization reactions of achiral dienes mediated by rhodium-complexes derived from enantiopure phosphine-phosphite (*P*–*OP*) ligands have been reported (*Org. Lett.* (**2016**) *18*, 2836-2839; see Figure 2). The highest performing ligand, which contains a TADDOL-derived phosphite fragment [TADDOL = (2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(diphenyl-methanol)], presented excellent catalytic properties for the desymmetrization of a set of achiral 1,4-dienes, providing access to the selective formation of a variety of enantioenriched secondary and tertiary alcohols (six examples, up to 92% ee).



Rh-mediated hydrogenative desymmetrizations

Fig. 2 – [Rh(*P*–*OP*)]-mediated desymmetrization of achiral 1,4-dienes

We have also reported (*Chem. Eur. J.* (**2016**) *22*, 10607-10613; see Figure 3) that, iridium(I) complexes of *P*–*OP* ligands efficiently catalyze the enantioselective hydrogenation of diverse seven-membered C=N-containing heterocyclic compounds (eleven examples; up to 97% *ee*). The observed sense of stereoselection was rationalized by means of DFT calculations.



Ir-P-OP-mediated asymmetric hydrogenations of seven-membered heterocyclic derivatives

Fig. 3 – [Ir(*P*–*OP*)]-mediated hydrogenation of seven-membered C=N-containing heterocycles

Another important project of our research group entails the development of strategies to generate

enantioselective supramolecular catalysts that incorporate regulation mechanisms for the catalytic site (*Chem. Commun.* (**2016**) 11038-11051).

The backbone of these catalysts is based on a privileged structure from asymmetric catalysis that also contains a remote regulation center. The regulation mechanism is triggered by a regulating agent (RA) that interacts with the ligand *via* supramolecular interactions at the remote site to create a particular catalytic system that incorporates subtle peculiarities in the geometry of its active site depending on the RA used.

We have reported that different polyether binders (alkali metal, alkaline earth metal and lanthanide salts) as regulation agents have a pronounced effect in the outcome of allylic substitution reactions and enhance the catalytic properties of palladium complexes derived from enantiopure bisphosphite ligands (*Organometallics* (**2016**) *35*, 528-533; see Figure 4). The addition of RbOAc or $M(OTf)_x$ ($M = Mg^{2+}$, La^{3+} or Ho^{3+}) led to positive effects in enantioselectivity (by up to 16% ee) for the allylic substitution reactions. These ligands coordinated in the usual *cis*- or in an unprecedented *trans*-fashion to the palladium center, depending on the phosphite group, and presented different reactivity in the allylic substitutions.

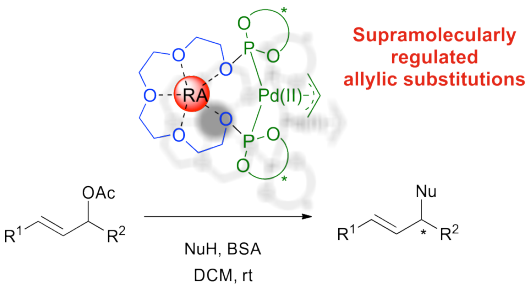


Fig. 4 – Supramolecularly regulated allylic substitutions

Articles

"A Practical Synthesis of Rhodium Precatalysts for Enantioselective Hydrogenative Transformations"
Synthesis (**2016**) *48*, 997-1001
B. Balakrishna, A. Vidal-Ferran

"Stereoselective Rh-Catalyzed Hydrogenative Desymmetrization of Achiral Substituted 1,4-Dienes"
Org. Lett. (**2016**) *18*, 2836-2839
H. Fernández-Pérez, J. R. Lao, A. Vidal-Ferran

"Asymmetric Hydrogenation of Seven-membered C=N-containing Heterocycles and Rationalization of the Enantioselectivity"
Chem. Eur. J. (**2016**) *22*, 10607-10613
B. Balakrishna, A. Bauzá, A. Frontera, A. Vidal-Ferran

"Supramolecularly Fine-regulated Enantioselective Catalysts"
Chem. Commun. (**2016**) 11038-11051
M. Vaquero, L. Rovira, A. Vidal-Ferran

"Palladium-Based Supramolecularly Regulated Catalysts for Asymmetric Allylic Substitutions"
Organometallics (**2016**) *35*, 528-533
L. Rovira, H. Fernández-Pérez, A. Vidal-Ferran

"Correlation between the Selectivity and the Structure of an Asymmetric Catalyst Built on a Chirally Amplified Supramolecular Helical Scaffold"
J. Am. Chem. Soc. (**2016**) *138*, 4908-4916
A. Desmarchelier, X. Caumes, M. Raynal, A. Vidal-Ferran, P. W. N. M. van Leeuwen, L. Bouteiller