Vidal Research Group

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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, using versatile covalent chemistry, 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.

Catalysis is an exciting and competitive area of chemistry in which to work, as it enables unique and selective pathways for the conversion of simple compounds into complex molecules with minimal energy consumption and waste production (all key requirements in modern synthetic chemistry). Asymmetric catalysis in particular is among the most fascinating and challenging areas of modern organic chemistry and, in fact, the use of catalysts to control three-dimensional structures of products, including enantiomeric selectivity, constitutes both a challenge and an opportunity. The ongoing research aims at the design and synthesis of efficient enantioselective catalysts for transformations of interest, and at the study of their use to prepare optically enriched products of biological, pharmaceutical or agrochemical interest. Critical aspects of this work include *modular design* of the catalysts; use of *versatile procedures* (organic and inorganic transformations, or supramolecular processes) to synthesize them; incorporation of *regulatory mechanisms* for their active site geometry; and *computational study* of their catalytic cycles (by establishing scientific collaborations).

Over the past few years, the research group has developed highly efficient strategies for the synthesis of 1,2-*P*–*OP* ligands from enantiopure epoxides in two steps: *ring opening of enantiopure epoxides* with phosphorus nucleophiles and *O-phosphorylation of the resulting phosphino alcohol* with a chlorophosphite in the presence of a base.

We have demonstrated that iridium(I) complexes of enantiomerically pure phosphine-phosphite ligands ([Ir(Cl)(cod)(1,2-*P*–*OP*)]) efficiently catalyze the enantioselective hydrogenation of diverse C=N-containing heterocyclic compounds (benzoxazines, benzoxazinones, benzothiazinones, and quinoxalinones; see Figure 1). High enantioselectivities were obtained (25 examples, up to 99% ee) and a substrate-to-catalyst ratio as high as 2000:1 was reached.

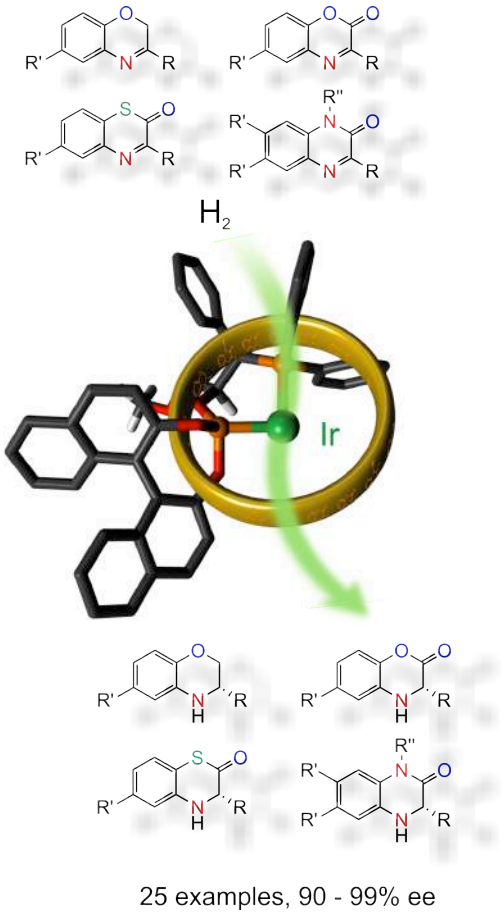

Fig. 1 – *Asymmetric Hydrogenation of Diversely Substituted C=N-Containing Heterocycles*

The research group has also been working in the design, preparation and catalytic studies of narrow bite-angle 1,1-*P*–*OP* ligands. A series of new ligands have been synthesized by a two-step method. The key intermediate was prepared by an unprecedented asymmetric carbonyl reduction of a phosphamide using the CBS (Corey-Bakshi-Shibata) catalyst. The topology of these ligands (a configurationally stable stereogenic carbon with two heteroatom substituents), and their small bite-angle (created by the close proximity of the two ligating groups to the metal center), together provide a rigid asymmetric environment around this center, enabling high stereoselectivity in hydroformylations and hydrogenations of an array of structurally diverse substrates (Figure 2).

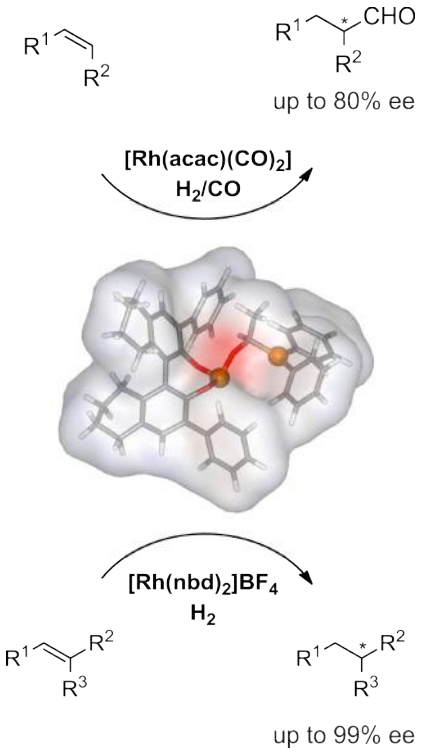

Fig. 2 – *Narrow Bite-Angle* P–OP *Ligands for Asymmetric Hydroformylation and Hydrogenation*

The group has recently devised a strategy for generating a set of supramolecular ligands that resemble a privileged structure and offer an active center that can be regulated to create a range of closely geometrically related active sites. The main advantage of this approach is that the geometry of the catalytic site can be modified through supramolecular interactions.
We have reported the design and preparation of supramolecular bis(phosphite) ligands (Figure 3), in which the two binding phosphite groups are separated by a polyether spacer that serves as the "regulation" site of catalytic activity. Small amounts of achiral polyether binders (alkali metal salts) are employed to enhance the enantioselectivity in the hydroformylation of an array of diversely substituted substrates (increase of up to 62% *ee* for vinyl acetate) mediated by chiral rhodium complexes derived from the α,ω-bis(phosphite)-polyether ligands. To the best of our knowledge, this study represents an unprecedented successful example of positive regulation of enantioselectivity in hydroformylations.

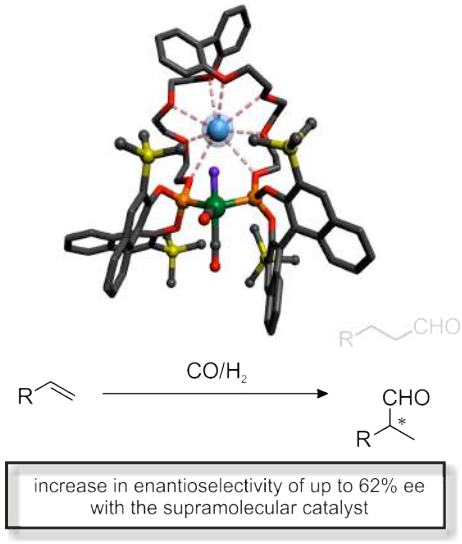

Fig. 3 – B*is(phosphite) Ligands with Distal Regulation: Application in Rhodium-mediated Asymmetric Hydroformylations.*

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 (Patent application submitted).

Articles

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Org. Lett. (**2013**) *3634-3637*
H. Fernández-Pérez, J. Benet-Buchholz, A. Vidal-Ferran

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Chem. Commun. (**2013**) *10666-10675*
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