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 relevance. Designing modular catalysts with versatile synthetic procedures, and performing computational analyses of the catalytic event, are key elements in our strategy.

Two main objectives have been pursued within the group: In the first instance, we have aimed to develop highly modular enantiopure *P*–*OP* ligands for asymmetric organometallic catalytic synthesis. Secondly, we have aimed to devise strategies to generate a set of supramolecular enantiopure ligands, which resemble a privileged structure yet at the same time offer a range of closely related geometrically active 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. The performance of the catalysts derived from these ligands has been tuned *via* modification of the electronic and steric properties of each molecular fragment (see Figure 1). To date, these *P*–*OP* ligands have been applied to rhodium- and iridium-mediated asymmetric hydrogenations (*Eur. J. Org. Chem.* (**2015**), *36*, 5293-5303), rhodium-mediated asymmetric hydroformylations and palladium-mediated allylic substitution reactions.

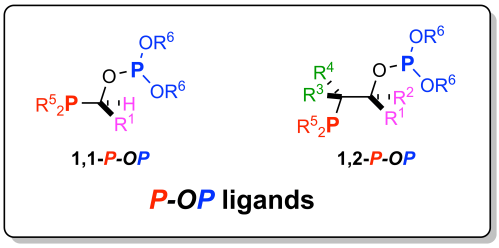

Fig. 1 – Modular *P*–*OP* ligands in the studied enantioselective transformations

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, an unprecedented strategy for obtaining highly enantioenriched sulfoxides based on a hydrogenative kinetic resolution using rhodium complexes of *P*–*OP* ligands as catalysts was developed (*Org Lett.* (**2015**), *17*, 4114-4117). This methodology was applied to a set of racemic aralkyl or aryl vinyl sulfoxides and allowed the isolation of both recovered and reduced products in excellent yields and enantioselectivities (up to 99% and 97% ee, respectively; 16 examples, see Figure 2). The easy availability of racemic vinyl sulfoxides, together with the excellent catalytic profile of the catalyst derived from *P*–*OP* ligands, makes this synthetic methodology a valuable synthetic entry for enantiopure (or highly enantioenriched) sulfoxides, which have proven to be efficient chiral ligands as well as valuable precursors in organic and pharmaceutical chemistry.

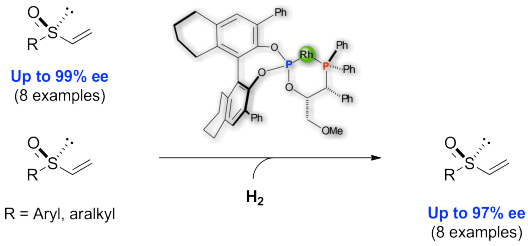

Fig. 2 – [Rh(*P*–*OP*)]-mediated asymmetric hydrogenative kinetic resolution of vinyl sulfoxides

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. 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. Small amounts of polyether-binder RAs were shown to regulate the activity of the catalysts for asymmetric hydroformylations and hydrogenations by biasing the distribution of enantiomers, as evidenced by the fact that the rhodium complexes of a ligand and RA enabled an increase in the enantioselectivity of up to 82% ee (*Chem. Eur. J.* (**2015**), *21*, 11417-11426, see Figure 3). Computational studies suggested that the increase in enantioselectivity provided by the RAs arose from adaptation of the P−Rh−P bond angle (*β*) to the particular requirements of the substrate.

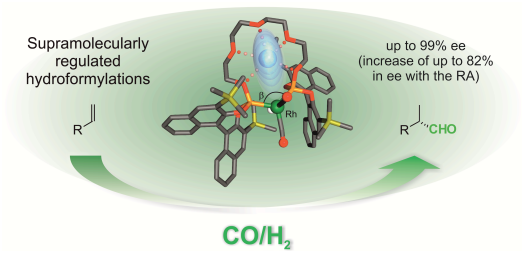

Fig. 3 – Supramolecularly regulated catalysts for asymmetric hydroformylations and hydrogenations

We also pursued to assess our supramolecular regulation methodology in the rhodium-mediated asymmetric hydroformylation of heterocyclic alkenes. For such purpose, we synthesized new supramolecularly regulated bisphosphite ligands incorporating an enantiomerically pure BINOL unit in the regulation site. We then showed that the inclusion of this motif reinforced the

regulation ability of the catalysts and led to efficient hydroformylation catalysts for a number of heterocyclic olefins providing high regio- and enantio-selectivities (up to 93% ee, see Figure 4). The outcome of the asymmetric hydroformylation could be exquisitely regulated by choosing the appropriate RA with an increase in the enantioselectivity, the reversal of the regioselectivity, or the complete suppression of one byproduct. (*J. Org. Chem* (**2015**), *80*, 10397-10403).

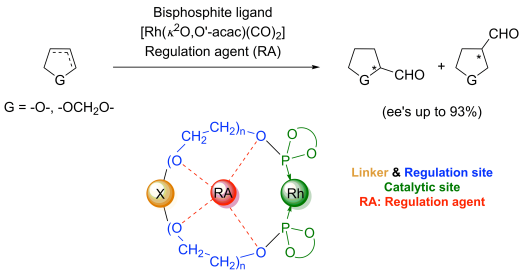

Fig. 4 – Asymmetric hydroformylation of heterocyclic olefins mediated by supramolecularly regulated bisphosphite ligands

As a continuation of our studies, we expanded our initial design to cyclic crown-ethers. Our new design encompassed a conformationally stable biaryl bisphosphine as the catalytic site and a crown ether unit as the remote regulation site (Fig. 5a). We envisaged that binding of a RA to the crown ether motif via supramolecular interactions could modulate the catalyst performance by modifying the bite angle *β* of the catalytic metal center (Fig. 5b). These new ligands enabled very good catalytic activity in rhodium-mediated asymmetric hydrogenations at low catalyst loadings (0.5 mol%), while the enantioselectivity remained moderate (up to 67% ee) (*Tetrahedron* (**2015**), *71*, 4490-4494). Moderately positive regulation effects for the enantioselectivity of the hydrogenation reactions were obtained as a result of the combination of the appropriate bisphosphine ligand and regulation agent.

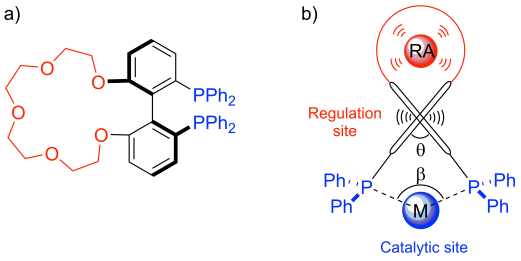

Fig. 5. a) Design of supramolecular bisphosphines with a remote regulation for asymmetric catalysis; b) Simplified representation of the regulation mechanism.

Articles

"Enantiopure Bisphosphine Ligands with Appended Crown Ether Groups as Regulation Sites for Rh-mediated Hydrogenations"
Tetrahedron (**2015**), *71*, 4490-4494
H. Fernández-Pérez, I. Mon, A. Frontera, A. Vidal-Ferran

"Supramolecularly Regulated Ligands for Asymmetric Hydroformylations and Hydrogenations"
Chem. Eur. J. (**2015**), *21*, 11417-11426
A. Vidal-Ferran, I. Mon, A. Bauzá, A. Frontera, L. Rovira

"Substrate Activation in the Catalytic Asymmetric Hydrogenation of *N*-Heteroarenes"
Eur. J. Org. Chem. (**2015**), *36*, 5293-5303
B. Bugga, J. L. Núñez-Rico, A. Vidal-Ferran

"Hydrogenative Kinetic Resolution of Vinyl Sulfoxides"
Org Lett. (**2015**), *17*, 4114-4117
J. R. Lao, H. Fernández-Pérez, A. Vidal-Ferran

"Diarylamino-substituted Tetraarylethene (TAE) as an Efficient and Robust Hole Transport Material for 11% Methyl Ammonium Lead Iodide Perovskite Solar Cells"
Chem. Commun. (**2015**), *51*, 13980-13982
L. Cabau, I. Garcia-Benito, A. Molina-Ontoria, N. F. Montcada, N. Martín, A. Vidal-Ferran, E. Palomares

"Asymmetric Hydroformylation of Heterocyclic Olefins Mediated by Supramolecularly Regulated Rhodium-Bisphosphite Complexes"
J. Org. Chem (**2015**), *80*, 10397-10403
L. Rovira, M. Vaquero, A. Vidal-Ferran

"Supramolecular Catalysis"
Book Chapter in *Reference Module in Chemistry, Molecular Science and Chemical Engineering.* Elsevier, (**2015**), 1-32 (ISBN: 978-0-12-409547-2)
P. Ballester, P. W. N. M. van Leeuwen, A. Vidal-Ferran