

## Perspectives in Modern Asymmetric Catalysis

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### Editorial

Asymmetric catalysis is nowadays a fundamental methodology for the preparation of chiral compounds whose demands is continuously growing in different fields of chemistry. Since the pioneering works in mid-60's of Knowles and Noyori on the asymmetric hydrogenation of olefins and ketones promoted by ruthenium/chiral diphosfine complexes, a wide portfolio of reactions have been developed in their enantioselective version thanks to the identification of the most suitable metal-chiral ligand combinations. With the aid of mechanistic studies, an impressive number of ligands with different coordinating groups and large structural diversity have been synthesized and high levels of stereocontrol achieved by careful tuning of their steric and electronic properties. However, in still limited cases high productivity, broad substrate scope, functional group tolerance and cost of the catalyst have fulfilled the requirements for industrial applications so that the search for new and more efficient catalytic systems remains an active topic in the field.

In the last decade organocatalysis, in which small organic molecules act as catalytically active species, has explosively grown in view of its operational simplicity, the possibility to functionalize carbonyl compounds without any substrate pre-activation and the identification of different activation modes as a basis for rational design of more active catalysts and discovery of novel reactivity. Initially perceived as a complementary approach to the traditional transition-metal based asymmetric catalysis, organocatalysis is today steadily moving as a real discipline toward its mature stage.

In the “sustainable development” era the scientific community is faced with the need to reduce the costs, the toxicity and the amount of waste related with chemical synthesis, but reconsideration of the existing productive processes often proved to be not sufficient to meet the goal so that innovative synthetic strategies and conceptual breakthroughs are greatly expected. Although asymmetric catalysis is a “green” methodology by itself, in accordance with 9<sup>th</sup> principle of green chemistry, further improvements are possible and extensive search for non-toxic metals and reaction media, more recyclable catalysts and solvents as well as more efficient reactor technology has opened new opportunities in setting effective solutions.

As selected examples, the fast expansion of stereoselective reactions promoted by complexes with the abundant, safe and economical iron metal and greater availability of Cu- and Ir-catalysts provide not only promising alternatives to precious noble metals but have also enlarged the range of applications to include new substrates and nucleophiles. The grafting of active ligands on magnetic nanoparticles or polymers with switchable solubility to give easily recoverable and recyclable catalysts and the use of water as biocompatible solvent in “on water” protocols with insoluble catalysts and reagents are other interesting approaches likely to increase in the future.

In a long term vision, the added value of “green chemistry” can be recognized in the emerging of new general concepts with potentially high impact on the blossoming of a modern way to thinking and planning organic synthesis.

Taking inspiration from nature in which complex molecules from simple precursors are formed by means of coupled action of different enzymes, multicatalysis is attracting burgeoning attention as a powerful synthetic paradigm for the construction of multiple stereogenic centers through consecutive reactions in a single flask. Obvious advantages in the absence of derivatization steps, the reduction of waste generation related with purification of intermediates and the simplification of product isolation for the predominance of single stereoisomers make multicatalytic processes very effective for high atom economy and lowered environmental factor.

In this context, several cascade sequences promoted by secondary amines, able to react *via* enamine or iminium intermediate, or by multicatalytic systems, in which distinct organocatalysts work with different activation modes, have been recently developed and their number is expected to quickly increase. The synthesis of tetra-substituted cyclohex-1-ene carbaldehydes from a multicomponent reaction of aldehydes,  $\alpha$ ,  $\beta$ -unsaturated aldehydes and  $\beta$ -nitrostyrenes in the presence of the sole prolinol Jorgenson's catalyst through a Michael/Michael/aldol sequence is a seminal example of the application of the strategy, that was successfully extended to the preparation of other carbocyclic structures with up to four new stereogenic carbons by using the same catalyst in combination with chiral thioureas or *N*-heterocyclic carbenes. In the same way, the orthogonal reactivity of proline/Mac Millan's imidazolinone binary system gives a versatile platform for double functionalization of the ethylenic bond of enals with a broad range of both nucleophiles and electrophiles also allowing the access to all diastereomers by choosing the suitable combination of catalysts configurations.

In a different approach, transition metal complex-organocatalyst hybrids could enable the access to challenging molecular frameworks through unprecedented transformations not possible using a single catalyst alone. The specific activation of alkynes or allenes by gold (I)-catalysts to give a variety of stereoselective cyclization reactions, in some cases also with formation of C-heteroatom bonds, in the presence of an organocatalyst as source of stereocontrol and the enantioselective allylation of  $\alpha$ -branched aldehydes to create an all-carbon quaternary stereogenic center by using a Pd/BINOL-derived phosphoric acid system are outstanding examples in this relatively young area.

The high enantioselectivity displayed by BINOL-derived phosphoric acids, alone or in conjunction with transition metal complexes, has been associated with their Brønsted acid character that

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leads to the formation of chiral anions able to exert stereocontrol by means of strong ion-pairing with cationic intermediates generated in the reactions. For the large occurrence of cationic species in many chemical transformations this mode of chirality transfer, categorized as asymmetric counterion directed catalysis, could provide a highly general strategy to achieve stereoselectivity. Beyond Brønsted acids based on the 1,1'-binaphthyl privileged scaffold, other systems in which simple anions as halides or carboxylates are rendered chiral by hydrogen bonds with enantiopure thiourea catalysts begin to appear in literature.

The renewed interest in ion-pairing, previously mainly focused on chiral ammonium quaternary salts used in phase-transfer catalysis, also opens new possibility in the design of novel supramolecular catalysts deriving from self-assembly of a chiral amine and a chiral acid, each one with its own organocatalytic activation potential, driven by electrostatic attraction. Cooperative effects could be delivered in well-

ordered transition states in which all the reaction partners are held in close proximity by ionic bonds, ultimately resulting in improved reactivity and stereoselectivity.

Although the avoidance of possible interferences between multiple catalysts and/or reagents is often a difficult task, in some instances resolved using sophisticated site-isolation techniques, mult catalysis offers great opportunities for substantial advances in the synthesis of stereogenically complex structures. Combinatorial libraries of supramolecular catalysts, built on the basis of different non-covalent interactions also including ion-pairing, can contribute to the identification of active and versatile catalysts with unexpected molecular frameworks and simplified synthesis with respect to the covalent analogues. Asymmetric catalysis will surely continue to be an exciting research field and it will play its part in addressing the demands of green chemistry with the development of novel concepts, new chemical reactivity and more sustainable processes.