

CAFC9: 9th Congress on Catalysis Applied to Fine Chemicals

Selective precious metal catalysts play key roles in value added fine chemicals synthesis

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Fine chemicals have been defined in many ways, but one definition would be that they are chemical products with specific properties which give them a high added value. As a consequence these molecules are, in general, polyfunctional molecules that require highly selective synthetic methods. Therefore, catalysis plays a crucial role in fine chemicals synthesis, and any improvements in catalytic performance can have a very positive impact on the fine chemicals industry.

The Congress on Catalysis Applied to Fine Chemicals (CAFC) is devoted to the application of any type of catalyst (homogeneous, heterogeneous or enzymatic) to the synthesis of fine chemicals, with special emphasis on selectivity. Previous conferences in this series have been held in The Netherlands (2003), Germany (2005) and Italy (2007). The latest, CAFC9, was held in Zaragoza, Spain, from 13th to 16th September 2010 (1), in the magnificent Paraninfo Building of the University of Zaragoza. It was organised by the Heterogeneous Catalysis in Selective Organic Synthesis Group at the university, with financial support from the Spanish Council for Scientific Research (CSIC), the University of Zaragoza and the Government of Aragón.

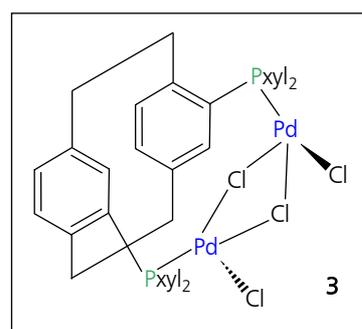
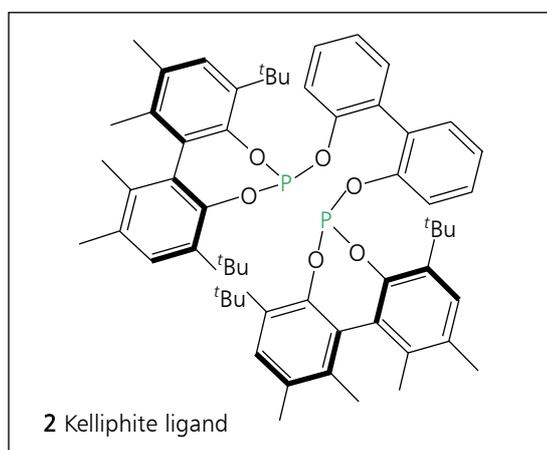
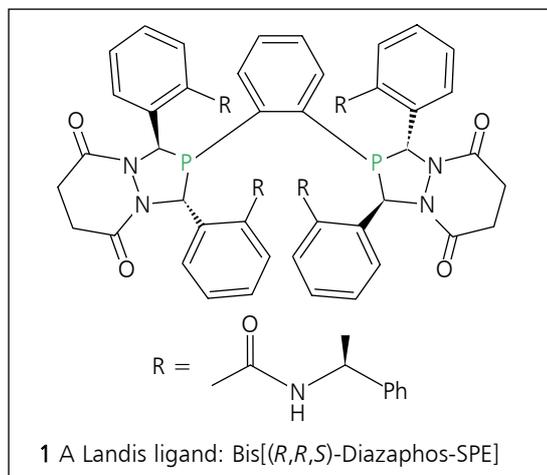
The scientific programme consisted of nine sessions, with four plenary lectures, five keynote lectures, and 31 oral communications, as well as two poster sessions. Overall, around 125 participants from both academia and industry in 20 countries attended this event. Researchers involved in areas from the synthesis of target molecules in the pharmaceutical industry to catalyst development were able to discuss their work and share their experiences. The contributions covered a wide range of work in fields such as enzymatic catalysis, organocatalysis, solution-phase and supported complexes of a large variety of metals, heterogeneous acids and bases, supported metals, and less conventional subjects such as the application of neoteric solvents (ionic liquids, supercritical carbon dioxide (scCO₂), etc.), continuous flow reactions, or metal–organic frameworks. However, for this review only relevant works involving

the use of platinum group metals (pgms) and gold have been selected. The review has been divided into three categories: homogeneous catalysis, heterogeneous catalysis, and metal nanoparticles, according to the type of catalytic system, although the boundaries between these three categories are not clear in some cases.

Homogeneous Catalysis

A good number of contributions, many of them from industrial participants, dealt with the use of precious metals in the form of homogeneous catalyst complexes. Walter Leitner (RWTH Aachen University, Germany) demonstrated in the opening plenary lecture how scCO_2 can be successfully used to carry out continuous-flow reactions, either as the only reaction medium or as part of a biphasic system (liquid-liquid or liquid-solid). The tunable properties of scCO_2 as a solvent allow the efficient design of catalytic reactions, such as the isomerisation of allylic alcohols catalysed by rhodium or ruthenium complexes with phosphines bearing perfluorinated chains. Integrated processes such as the ruthenium-catalysed conversion of levulinic acid (4-oxopentanoic acid) into 2-methyltetrahydrofuran can also be treated in this way. Several examples of biphasic systems of scCO_2 with another liquid phase were also presented. Ionic liquids, such as 1-butyl-3-methylimidazolium hexafluorophosphate, $[\text{bmim}][\text{PF}_6]$, can be used as a carrier for chiral iridium–phosphinooxazoline or rhodium–quinaphos complexes, active in the enantioselective hydrogenation of imines and alkenes, respectively. It is also possible to immobilise the ionic liquid phase on solids, improving the life of the catalyst. Other liquid phases for biphasic systems can be poly(ethylene glycol) (PEG) or water, provided that a suitable ligand is used to improve the solubility of the complex.

Matt Clarke (University of St Andrews, UK) described the development of carbonylation processes to obtain building blocks for biologically active chiral compounds. The ligand and the method of catalyst preparation play extremely important roles in determining catalyst performance. For example, rhodium-catalysed hydroformylation of alkenes can be carried out with high enantioselectivity using Landis ligands (diazaphospholanes), **1**, or Kelliphite ligand (a diphosphite), **2**, depending on the substrate. It was also shown how a dipalladium complex with a chiral diphosphine Xyl-Phanephos, **3**, is able to efficiently

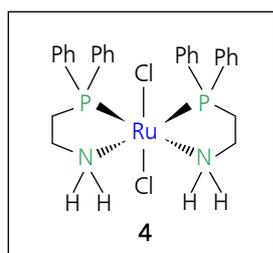


catalyse the enantioselective hydroxy- and alkoxy-carbonylation of alkenes for the production of chiral acids and esters.

Christian Müller (Eindhoven University of Technology, The Netherlands) presented work in which the rhodium-catalysed hydroformylation of alkenes was integrated in sequence with a cyclisation reaction to construct complex molecular

structures based on bicyclic and tricyclic imidazole derivatives. Several rhodium catalysts with phosphorus-containing ligands were used to catalyse the hydroformylation reaction. The cyclisation step was simultaneously accelerated by microwave irradiation, reaching overall yields higher than 95%.

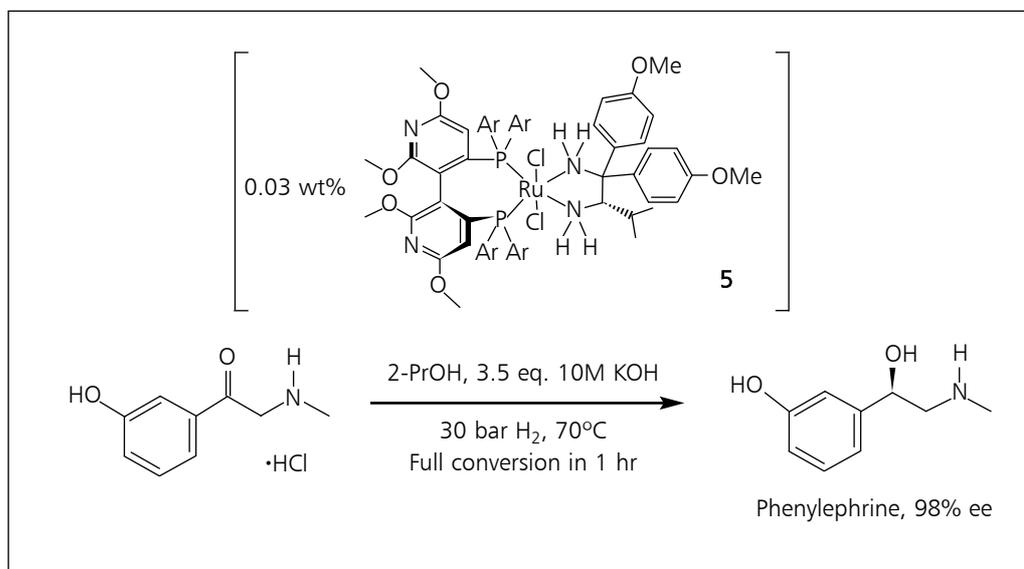
Homogeneous hydrogenations catalysed by different metal complexes were also discussed. Lionel Saudan (Firmenich SA, Switzerland) showed in a keynote lecture how ruthenium complexes with nitrogen–phosphorus ligands, such as **4**, could reduce esters to alcohols using a low catalyst loading (0.01–0.05 mol%) under mild conditions. The methodology can be applied to a wide range of substrates with almost quantitative yields and it even allowed the selective hydrogenation of esters in the presence of C=C double bonds with over 95% conversion.



Hans Guenter Nedden (Johnson Matthey, Catalysis and Chiral Technologies, UK) described the industrial application and optimisation of Noyori's enantioselective ketone hydrogenation methodology. In one process example, the active pharmaceutical ingredient phenylephrine was obtained (**Scheme 1**), using a [Xyl-P-Phos RuCl₂ Daipen] catalyst, **5**, without the need for protecting groups, used to date in manufacturing processes.

Laurent Lefort (DSM, The Netherlands) presented two different pathways to obtain chiral amines, which are also important building blocks in the synthesis of high value-added products of industrial interest. Firstly, the enantioselective hydrogenation of enamines with a new rhodium–phosphoramidite chiral catalyst was applied to the synthesis of an anti-obesity drug intermediate. Secondly, the asymmetric reductive amination of β -ketoesters to the corresponding β -amino acid derivatives was achieved by means of a ruthenium–diphosphine catalyst.

An enantioselective hydrogenation, reported in a keynote lecture by Rocco Paciello (BASF, Germany), was the first step in an efficient three-step route to L-menthol from citral (3,7-dimethyl-2,6-octadienal). The conjugated C=C double bond of the α , β -unsaturated carbonyl compound was chemoselectively hydrogenated using a rhodium–chiraphos catalyst. Opti-



Scheme 1

misation was possible by using a small amount of carbon monoxide to preserve the active species. This was verified by a density functional theory (DFT) mechanistic study.

Other enantioselective reactions, such as palladium-catalysed allylic substitution and ruthenium-catalysed cyclopropanation and transfer hydrogenation, were presented in several of the posters.

Heterogeneous Catalysis

In one of the plenary lectures, Hermenegildo García (Instituto de Tecnología Química, Spain) showed how metal–organic frameworks (MOFs) can act as reusable heterogeneous catalysts for the synthesis of fine chemicals. He proved that, in some cases, MOFs can perform better than the analogous transition metal catalysts in solution or than related zeolitic materials, due to their large surface area, high metal density, site isolation and hindered aggregation. In one of the examples, a palladium 2-hydroxypyrimidinolate MOF (**Figure 1**) was able to carry out the oxidation of allylic alcohols to aldehydes in an aerobic atmosphere with 99% conversion and 74% selectivity. No palladium leaching was detected and the solid catalyst could be recovered and reused in several consecutive runs.

Several authors showed the use of mesoporous solids as supports for transition metal complexes.

Marie Genelot (Institut de Recherches sur la Catalyse et l'Environnement de Lyon (IRCELYON), France), in her keynote lecture, described the preparation of several quinolones and indoxyls through a carbonylative Sonogashira coupling/cyclisation sequence catalysed by palladium complexes immobilised on mesoporous SBA-type silica solids. Together with the palladium catalyst, an immobilised amine or an immobilised phosphine had to be used in order to selectively obtain a six-member or a five-member *N*-heterocycle, respectively (**Scheme II**). Palladium leaching was detected and a study of different reaction parameters (solvent polarity, surface treatment and type of catalyst) was carried out to try to reduce this. Suman Sahoo (Stockholm University, Sweden) reported the immobilisation of rhodium complexes onto several silica MCM and SBA mesoporous solids *via* two strategies: covalent bonding of the *N*-heterocyclic carbene ligand or hydrogen bonding through a sulfonic group on the phosphine ligand. The catalysts were used to promote the isomerisation of allylic alcohols and the amination of aryl bromides with good activity. Other examples of immobilised complexes, including the ruthenium–BINAP–diamine system on graphite oxide and ruthenium-based Grubbs catalyst on mesoporous silica, were reported in the poster sessions.

Other supports were also used for the immobilisation of metals such as platinum, palladium or gold.

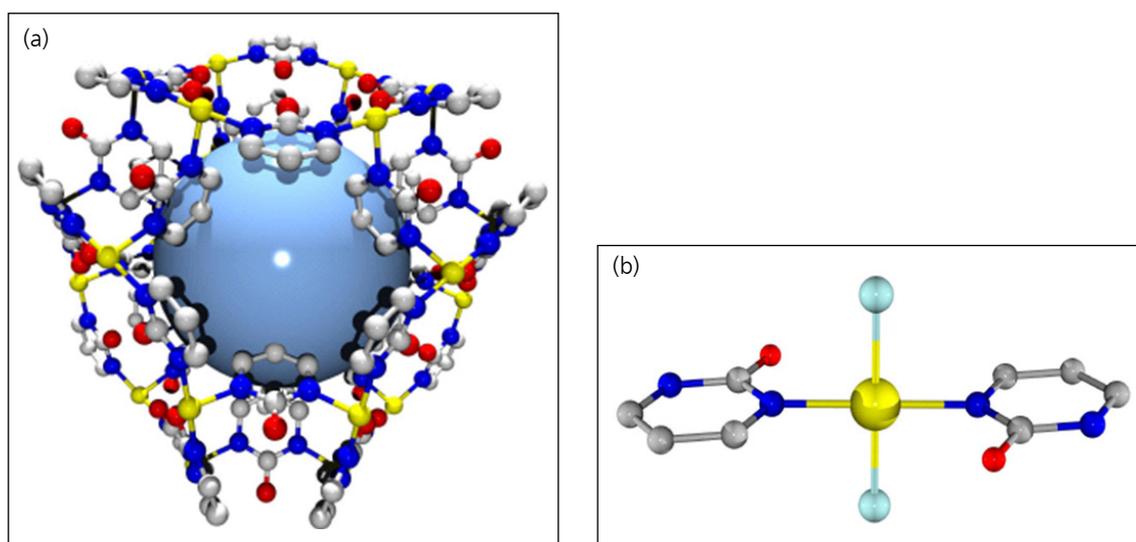
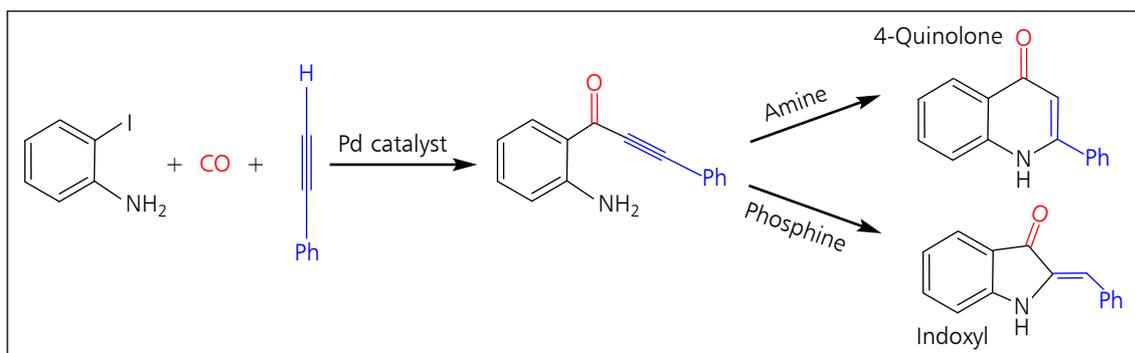


Fig. 1. (a) A palladium 2-hydroxypyrimidinolate metal–organic framework (MOF) used to catalyse efficient oxidation of allylic alcohols to aldehydes; (b) Palladium 2-hydroxypyrimidinolate subunit. Colour coding: blue = N, red = O, yellow = Pd, grey = C, light blue = Cl (Courtesy of Jorge A. Rodríguez Navarro, Department of Inorganic Chemistry, University of Granada, Spain)



Scheme II

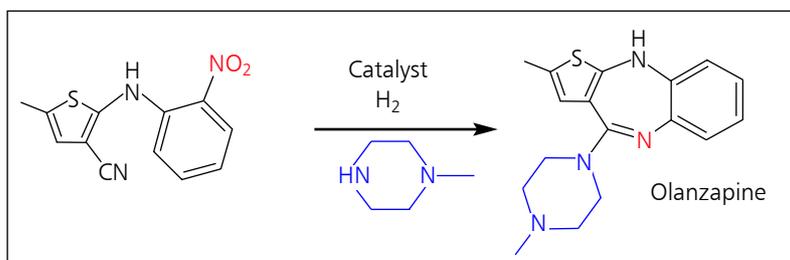
Gatla Suresh (Leibniz Institute for Catalysis, Germany) described the preparation of several palladium on titania (Pd/TiO₂) catalysts in order to accomplish the gas-phase acetoxylation of toluene. The influence of precursors, promoters, supports and pretreatment procedures on the reaction was studied. The highest catalytic performance was reached with a palladium-antimony catalyst supported on rutile, which gave a selectivity of 99%. TiO₂ was also used by Katharina Heidkamp (Institute of Agricultural Technology and Biosystems Engineering, Johann Heinrich von Thünen-Institute, Germany) as a support for gold and gold-platinum catalysts, which proved to be active for the oxidation of fatty alcohol ethoxylates to their corresponding carboxylic acids with molecular oxygen. Variable leaching of gold was detected for Au/TiO₂ depending on the preparation conditions. The presence of platinum in a bimetallic Au-Pt/TiO₂ catalyst improved the activity and reduced metal leaching. The screening of other support materials showed that the use of ceria (CeO₂) completely avoided gold leaching and gave very good activity (58 mmol min⁻¹ g_{Au}⁻¹) and selectivity (>99%) under optimised reaction conditions.

Antonio Leyva-Pérez (Instituto de Tecnología Química, Spain) also proposed the use of TiO₂, as well as of silica ITQ-2, for the immobilisation of platinum or palladium. A metal-acid bifunctional solid catalyst was obtained. This was able to promote a cascade process involving a chemoselective hydrogenation-cyclisation-amination reaction, to obtain the antipsychotics olanzapine (Scheme III) and clozapine.

A good number of examples of supported metals were also described in the poster sessions. There were several examples of oxidation reactions, including the oxidation of glucose using hydrogen peroxide (H₂O₂) and gold on alumina (Au/Al₂O₃) catalysts, the dehydrogenation of lignans using palladium on different supports (alumina, activated carbon and mesoporous silicas), and the aerobic oxidation of secondary alcohols using Pt/C. Suzuki and Heck coupling reactions with palladium catalysts were also described, and there were some examples of hydrogenation reactions.

Metal Nanoparticles

The use of nanoparticles was described in a number of oral communications and posters. In his keynote



Scheme III

lecture, Tamas Mallat (ETH Zurich, Switzerland) described the use of several rhodium and platinum nanoparticles supported on Al_2O_3 , SiO_2 or the mixed oxide and modified by cinchonidine or quinine molecules. These catalysts were tested in the enantioselective hydrogenation of several aliphatic and aromatic ketones, and gave enantioselectivities up to 94%. A detailed study of the particle size, crystallographic face and acid-base properties of the support showed the sensitivity of the catalytic performance to all these factors.

Takato Mitsudome (Osaka University, Japan) reported the deoxygenation of epoxides using alcohols as reductants and catalysed by gold nanoparticles stabilised on hydrotalcite. A wide range of epoxides can be deoxygenated to their corresponding alkenes with a selectivity of over 99% and a turnover number (TON) of up to 20,000. The catalysts were recovered by filtration and reused in several reaction cycles without loss of activity.

Pawel K. Plucinski (University of Bath, UK) presented the use of a continuous reactor containing magnetically entrapped nanocatalysts. Magnetite (Fe_3O_4) superparamagnetic nanoparticles were used as carriers to immobilise chiral complexes such as (*R,R*)-Rh-DUPHOS- SO_3 and (*R*)-Ru(OAc) $_2$ (BINAP) or palladium nanoparticles on the surface. The catalysts were tested for hydrogenations, Suzuki reactions and even a tandem Knoevenagel condensation-hydrogenation reaction, resulting in excellent catalytic performance.

Organic polymers can also be used to stabilise nanoparticles. Linda Zh. Nikoshvili (Tver Technical University, Russia) presented two methods of formation of nanoparticles in two types of nanostructured organic polymers: amphiphilic block polymers with poly(2-vinylpyridine) units and hypercrosslinked polystyrene. These polymers were prepared containing Pt, Pd, Ru, Au or bimetallic systems such as Pd-Pt, Pd-Zn, Pd-Au or Ru-Pt. After a complete characterisation of the catalysts, they were tested for the triple bond hydrogenation of dehydrolinalool (3,7-dimethyloct-6-ene-1-yne-3-ol) and for the selective oxidation of L-sorbose and D-glucose.

Françoise Quignard (The Institute Charles Gerhardt of Montpellier, France) described alginates (polysaccharides) as stabilisers for palladium nanoparticles. Palladium cations can be exchanged in ionotropic gels of alginates with divalent cations and then reduced to form the supported nanoparticles. The tex-

tural properties and particle size were highly dependent on the initial divalent cation in the alginate. The best performance for the Suzuki carbon-carbon coupling reaction was obtained with a black Pd-Cu/alginate catalyst (Figure 2) (2).

Eduardo García-Verdugo (Universitat Jaume I, Spain) reported the use of polystyrene-divinylbenzene copolymers (beads and monoliths) functionalised with imidazolium groups (similar to ionic liquids) as supports for palladium and gold nanoparticles, among other catalysts. As an example, supported palladium nanoparticles were tested as catalysts for Heck reactions. The functionalised polymers can be reused in several reaction cycles without loss of catalytic performance. Pasi Virtanen (Åbo Akademi, Finland) described the immobilisation of palladium nanoparticles in an ionic liquid phase supported on activated carbon cloth. The effect of alkaline modifiers on the catalytic activity of the solids in the hydrogenation of citral (3,7-dimethyloct-2,6-dienal) in a batch reactor was studied. The alkaline modifiers were able to enhance the activity and increase the selectivity to citronellal (3,7-dimethyloct-6-en-al).

Concluding Remarks

Selectivity issues (chemoselectivity, regioselectivity, stereoselectivity and enantioselectivity) are crucial in the synthesis of fine chemicals, and catalysis plays a key role. In the closing plenary lecture of CAFC9, Hans-Jürgen Federsel (AstraZeneca, Sweden) showed how catalysis in general, and in particular that involving precious metals, is a valuable tool in making the fine chemicals industry more sustainable,



Fig. 2. Black palladium-copper/alginate catalyst for Suzuki coupling (Reprinted with permission from (2). Copyright 2009 American Chemical Society)

both from an environmental and an economic point of view. Improvements to the predictability, scope, selectivity and customisability of catalytic methods will in turn increase the usefulness of catalysis even further, but for this to happen there is a need for a deeper scientific understanding of catalysts and catalytic processes. The CAFC series aims to address this need to the benefit of both the scientific community and industry.

As a summary of the Congress, a selection of contributions will be published in a special issue of *Catalysis Today* in 2011 (3). Finally, it was decided that CAFC10 will be held in Turku (Åbo) Finland in 2013.

References

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- 2 A. Primo, M. Liebel and F. Quignard, *Chem. Mater.*, 2009, **21**, (4), 621
- 3 *Catalysis Today*, Special Issue: 9th Congress on Catalysis Applied to Fine Chemicals (CAFC9), to be published in 2011

The Reviewers



José M. Fraile is currently a Research Scientist of the Spanish Council for Scientific Research (CSIC) in the Instituto de Ciencia de Materiales de Aragón (ICMA) at the University of Zaragoza, Spain. He obtained his PhD from the University of Zaragoza in 1992. He worked as a postdoctoral researcher in the École Nationale Supérieure de Chimie de Montpellier, France. His research interests focus on the preparation and application of heterogeneous catalysts based on metals such as copper, palladium, iridium, ruthenium, etc. for selective organic synthesis, mainly chiral catalysts for enantioselective processes.



Clara I. Herrerías is currently a lecturer at the University of Zaragoza, Spain. She obtained her degree and PhD from the same university under the supervision of Dr J. A. Mayoral and Dr J. M. Fraile. She worked as a postdoctoral researcher in Dr C.-J. Li's group at McGill University, Canada, and later, in Dr M. A. Pericàs' group at the Institute of Chemical Research of Catalonia, Spain. She is involved in the development of compatible heterogeneous catalysts based on metals including copper, palladium, titanium, etc. for multi-step reactions and in the synthesis and applicability of new multitopic chiral ligands, able to form complexes with several metals at the same time.