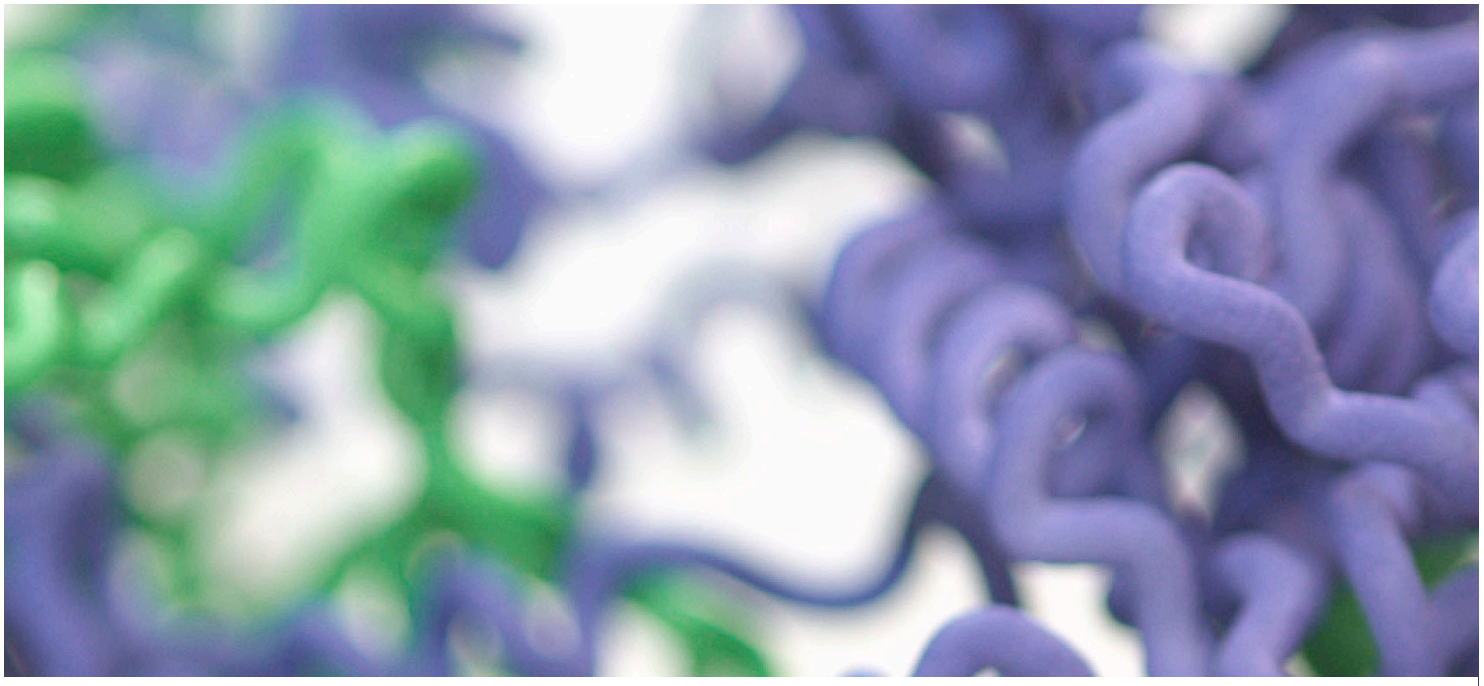

IRB BARCELONA

INSTITUTE FOR RESEARCH IN BIOMEDICINE

Advancing the frontiers of biomedical research

The Institute for Research in Biomedicine (IRB Barcelona) is an independent, non for-profit research center engaged in basic and applied biomedical science. The convergence of biology, chemistry, medicine, physics and computer science at IRB Barcelona provides a unique opportunity for the translation of basic biomedical research into innovation.

MAXPHOX

NOVEL COST SAVING CATALYSTS FOR ASYMMETRIC HYROGENATION OF ENAMIDES

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The Research Unit on Asymmetric Synthesis of IRB Barcelona has developed MAXPHOX, a new series of ligands capable of increasing the enantiomeric excess of certain asymmetric hydrogenation reactions up to a 99%ee (enantiomeric excess), using both low H2 pressure and temperature.

As an example, a member of the MAXPHOX family widely improves the current synthesis of Rotigotine from an 84 to a 99%ee, using 3 bar pressure.

CHALLENGE

Many natural products, including pharmaceutical compounds and agrochemicals are chiral. Therefore, they can exist as two different isomers (enantiomers) that, most of the times, show different biological action. The selective preparation of one enantiomer of a chiral compound is called asymmetric synthesis. This may be accomplished by the use of chiral reagents or auxiliaries and a plethora of well-developed examples of both approaches is widely reported.

Although in biological reactions the synthesis of only one enantiomer is widespread and easily achieved through the use of enzymes, in chemical industrial processes, the steroselectivity is not trivial. Moreover, the separation of optical isomers from a racemic mixture is sometimes difficult to achieve and extremely costly because the unwanted isomer must be wasted.

A way to overcome this bottleneck is by asymmetric catalysis which using a sub-stoichiometric amount of a chiral catalyst leads to the desired isomer with high enantiomeric excess.

TECHNOLOGY

MAXPHOX technology is a family of new molecular ligands which are the key fragments of new organometallic catalysts. The catalytic activity originates from the metal (different metals may be used), and the asymmetry of the metal-catalysed process is induced by the organic ligands attached to the metal. These organic structures act as chiral scaffolding, controlling the binding of substrates and their subsequent reaction paths through steric and electronic interactions.

The different catalysts allow asymmetric hydrogenation of many types of substrates. They conserve functionality in a wide range of organic solvents, being active at room-temperatures and low H2 pressures.

The MAXPHOX ligands are easily accessible in an enantiomerically pure form and of relatively low molecular weight, thus further increasing the industrial interest.

Asymmetric hydrogenation using such catalysts provides an alternative route to the synthesis of N-substituted aminotetralines.

Full description of the technology in:
"Highly Enantioselective Iridium-Catalyzed Hydrogenation of Cyclic Enamides" Angew Chem Int Ed Engl. 2016 Jul 4;55(28):7988-92

COMMERCIAL OPPORTUNITY

The novelty of these compounds over currently available technologies is in the one hand, the high retrieved yields and enantiomeric excesses of the products and on the other hand, the quite low H2 working pressures.

It represents a much cheaper alternative to the synthesis of N-substituted aminotetralines, from the hydrogenation of enamides.

The synthesis of the catalyst has been already scaled-up till hundreds of grams and by being modular it is expected to be easily further scaled-up.

The technology is patent-protected and available for licensing or co-develop projects.

CURRENT STAGE OF DEVELOPMENT

Up to the present, the MAXPHOX family is composed of 8 different ligands. There are several examples tested and documented covering a wide variety of substrates and conditions. The yield are quantitative and the enantiomeric excesses greater than 95%ee.

One example of the pharmacologically relevant application is an alternative synthetic route for the Rotigotine precursor (one of the dopamine agonists indicated for the treatment of Parkinson's disease) depicted in Fig. 1.

Using the MAXPHOXb catalyst, the reaction can be performed in **different solvents**, using **room temperature** and the requested **H2 pressure is drastically reduced to 3 bar.** Furthermore, the overall reaction retrieves a yield of 99%ee of the desired enantiomer:

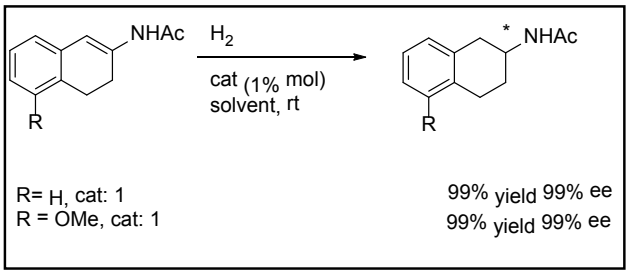

Fig 1 - Scheme of the molecular asymmetric hydrogenation of the Rotigotine precursor synthesis, as an example of application in asymmetric hydrogenation.

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