Chiral Magnetic Nanoparticles as Sustainable Asymmetric Catalysts

An investigation into the use of novel chiral magnetically-recoverable catalysts which have the potential to be used in cleaner and more efficient pharmaceutical drug syntheses

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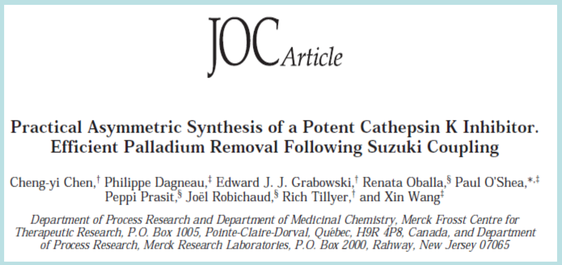
Making Pure Medicines – the synthesis of many drugs requires chiral metal catalysts that somehow need to be removed



JOC *Article*

Practical Asymmetric Synthesis of a Potent Cathepsin K Inhibitor. Efficient Palladium Removal Following Suzuki Coupling

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Figure 1. A journal article on the problems faced in removing palladium from an inhibitor of Cathepsin K, an enzyme thought to be involved in diseases characterised by excessive bone loss, such as osteoporosis.

Chirality is an important property of many drugs and natural products. A molecule is chiral if it is non superimposable on its mirror image. The molecule and its mirror image are called enantiomers and can have different chemical properties in a chiral environment. For example the commonly used drug ibuprofen; the drug is marketed as a racemate but the (*S*)- enantiomer has been found to be the active form both *in vivo* and *in vitro*. For ibuprofen, stereoselectivity is not so important as *in* vivo the (*S*)- enantiomer is converted to the (*R*)- enantiomer by an enzyme in the body, but the problem nicely illustrates the importance enantioselective reactions can play in the pharmaceutical industry.

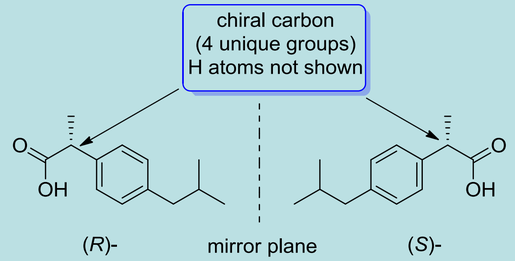


Figure 2. (Left) A packet of Nurofen Plus® containing the active ingredients ibuprofen and codeine. (Right) The (*R*)- and (*S*)- enantiomers of ibuprofen. The (*S*)-enantiomer is the active form. The dashes indicate that the methyl group points behind the plane of the poster. Making groups adopt a particular 3-D structure is crucial for many medicines.

Making chiral compounds frequently requires the use of a transition metal based homogeneous catalyst (the catalyst is in the same phase as the product). This results in the problem of removing the metal from the product before it can be used in pharmaceuticals. One idea is to have a biphasic reaction with the catalyst in one phase (e.g. aqueous) and the reagents in another (e.g. organic). However it is difficult to make the metal complex water soluble without affecting its other properties. A second strategy is to support the catalyst on an insoluble medium, and filter it off at the end.

Creating Chiral Nanomagnets – incorporating the asymmetric catalyst on an insoluble support to facilitate its recycling

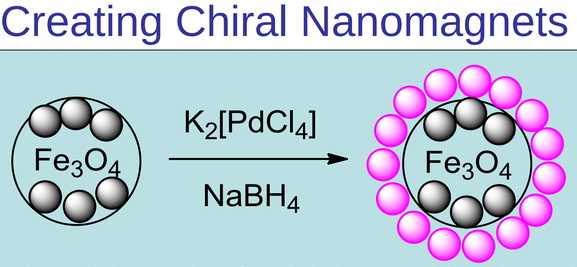


Figure 3. Preparation of Fe_3O_4/Pd nanoparticles. The Fe_3O_4 superparamagnetic core was synthesised and its surface was coated with palladium atoms following a reduction of the palladium(II) precursor with sodium borohydride. When an external magnetic field is applied, the magnetic core and surface palladium atoms are physically extracted out of solution. Research by other groups has shown that no molecular palladium species remain in solution.

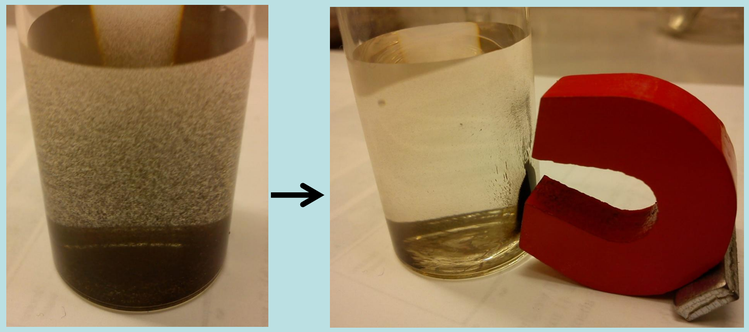
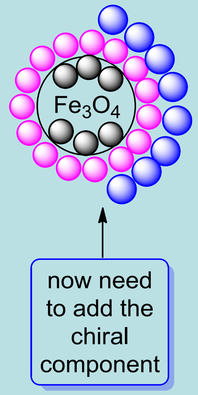
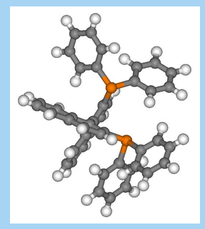


Figure 6. A photograph of the selective separation of our magnetic nanoparticles from the bulk solution using an ordinary household magnet.



Chiral phosphorus ligands are highly important in asymmetric catalysis. Noyori won a share of the 2001 Nobel prize in Chemistry for his work with the ligand BINAP (shown below and Figure 4).



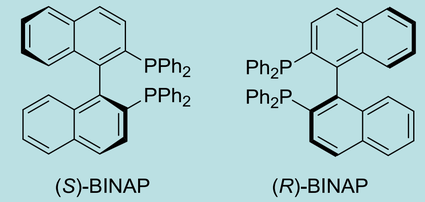


Figure 4. The structures of the two enantiomers of the chiral ligand, BINAP. Enantiopure compounds such as BINAP are commercially available but can be very expensive, therefore incorporating them into a catalyst which is easily recoverable is a very attractive prospect for industry.

Towards Pharmaceutical Targets – using the chiral nanomagnets to catalyse the synthesis of biologically-relevant molecules

A catalytic study has been reported which uses *non-chiral* ('achiral') palladium-coated magnetic nanoparticles. *Non-magnetic* nanoparticles with the enantiopure BINAP ligand have been used successfully in chiral hydrosilylation reactions of styrene. This project therefore aimed to combine both approaches and develop nanoparticles *which are both magnetic and chiral.* We would then extend the scope of the catalysis to chiral hydrogenation reactions. The synthesis of many pharmaceuticals involve an asymmetric reduction step, such as the preparation of the anticoagulant drug Warfarin. Therefore if the reactions can be directed towards such hydrogenations, they could prove to be a lucrative area of interest for industry.

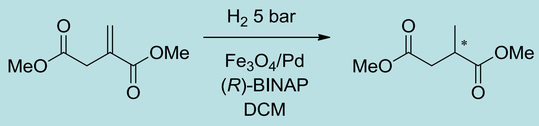


Figure 5. The asymmetric hydrogenation reaction of the model DMI substrate. DMI has been used as it is consistent with a standard biologically active molecule. A hydrogen gas pressure of 5 bar was required, therefore an autoclave vessel that could withstand such high pressures was needed (right image). The nanoparticles were removed from the reaction mixture by applying a magnetic field and decanting the product dissolved in the solvent.

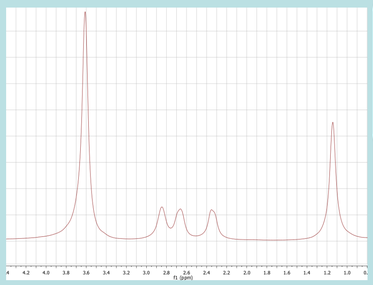


Figure 6. A ^{1}H NMR spectrum of the reduced DMI which formed in quantitative yield.

The use of chiral magnetic nanoparticles as recoverable asymmetric catalysts is an exciting new idea for both academia and industry. There is great potential for research in this field. One possible idea the research group has had is to use fluorescent ligands on the transition metal catalyst, this could provide an easy method of analysing accurately the % of catalyst remaining in solution and may help to explain the mechanism of catalysis which is currently not understood.

References and Acknowledgments

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