

Project Title:	Gaining Selectivity Control in Homogeneous Catalytic Ester Formation and Reduction with Multi-Nuclear High Resolution FlowNMR Spectroscopy
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Project Summary

The catalytic reduction of esters to alcohols is an exciting recent development of homogeneous catalysis with a clear potential for significant industrial impact. If only a fraction of the current industrial reduction reactions using stoichiometric hydride reagents (e.g. NaBH₄, LiAlH₄, DIBAL, etc.) could be replaced with highly active and selective catalysts utilising H₂, the environmental benefits would be enormous. Hydride reductions have complex and often hazardous work-up procedures that generate large amounts of waste, while homogeneous catalytic reductions are operationally simple, clean reactions with 100% atom economy that require little to no work-up.

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However, the potential of ester reduction catalysts can only be exploited if they can be shown to be a reliably superior choice to established technologies, and some important hurdles remain before the technology can be operated at full potential in an industrial environment. In particular, most homogeneous ester hydrogenation catalysts operate with a bifunctional mechanism under strongly basic conditions, which limits applications on chiral substrates (which often are prone to racemization) and substrates with even mildly acidic functional groups (e.g. phenols, malonates...). Currently there exists limited understanding of the mechanism and how reaction conditions (e.g. pH, water, solvent, base, deactivation/inhibition) affect the catalytic cycle and product distribution obtained. Empirical optimisation approaches are being pursued to improve the technology, but a rational, mechanism-guided investigation offers the opportunity to solve these key challenges. An understanding of the reaction pathway also promises to bring about new reactivity and allow capturing key intermediates to achieve new transformations. For instance, ester reduction to aldehyde, amide reduction to amine, and the reverse reactions of coupling alcohols/amines to esters/amides all represent highly sought-after transformations that are difficult to achieve selectively with existing catalysts due to a lack of mechanistic understanding.

Understanding the generation and structure of the key hydride intermediates might allow devising new catalysts that operate under milder hydrogen transfer conditions rather than with elevated H₂ pressure and strong bases.

Bath's Dynamic Reaction Monitoring (DReaM) Facility offers a unique combination of complementary operando techniques currently comprising multi-nuclear FlowNMR, head-space MS, liquid phase MS, UV-vis, and HPLC. All of these are part of a fully integrated and computer-controlled reaction monitoring system that is able to track reaction intermediates and products in real time to give comprehensive insight into complex reaction networks (such as ester reduction catalysis). Selective excitation pulse sequences can detect sub-micromolar traces of metal hydride intermediates, and we have recently implemented fast & quantitative ¹H/³¹P acquisition parameters to track ligands bound to the metal during catalysis. Advanced reaction progress kinetic analyses using variable time normalization analysis (VTNA) will be used to quantify deactivation phenomena to derive methods for minimizing/shunting inhibition pathways.

Johnson Matthey is a global specialty chemicals company and international leader in sustainable technologies and catalysis who will provide project support. The JM research centre in Cambridge (UK) is a state-of-the-art facility with more than thirty researchers and support personnel dedicated to the development of new catalytic solutions for the pharmaceutical, flavour and fragrances and agrochemical markets.

Sustainability Issues

Using highly active and selective catalysts utilizing H₂ would have enormous environmental benefits compared with current stoichiometric hydride reagents (e.g. NaBH₄, LiAlH₄, DIBAL, etc.). Hydride reductions have complex and often hazardous work-up procedures that generate large amounts of waste, while homogeneous catalytic reductions are operationally simple, clean reactions with 100% atom economy that require little to no work-up.