FINAL PUBLISHABLE SUMMARY REPORT – BIO PRE-ORGANOCATS

During the two-year duration of this project new information has been collected about aminocatalytic downstream intermediates. These catalytic intermediates had been identified before starting the project, but their existence was only used to explain the selectivity of aminocatalytic reaction. Now, we know much more about the thermodynamic and kinetic properties of these systems and this has led to two new improvements with high potential at both academic and industrial level.

1. New model of chiral recognition for the chiral resolution of lactols

We have discovered and understood how the chiral information is transferred from the aminocalyst to the rest of the molecule in the downstream intermediates. This new method of chiral recognition is of vital importance in all the aminocatalytic reactions described until today, but more importantly has led to the discovery of a new technology. The new model of chiral recognition has been used to design a clever way to differentiate chiral lactols in solution.

Lactols were identified as target substrates in the proposal of this project. Enantiomerically pure lactols are important in organic synthesis, as Prof. Darren Dixon has shown in several occasions. Prof. Dixon has used enantiomerically pure lactols in a large set of reactions to create new stereocenters selectively (Figure 1a). In addition, chiral lactones, oxidised derivatives of chiral lactols, are really important in fragrances, perfumery, and food industry (Figure 1b).

Racemic lactones are abundant and relatively cheap, so it is obvious that having a method to separate both enantiomers would be economically and environmentally better than having to synthesize them enantiomerically pure from scratch. But, until now, there were no good methods of separation for some of these lactones due to the difficulty of differentiating the corresponding enantiomers.

Thanks to the knowledge obtained with this project, we have now found an excellent technique to differentiate both enantiomers of lactols in solution. We are currently working in collaboration with Prof. Livingston (Chem. Eng. Imperial College) to develop an engineering solution to separate lactols at large scale.

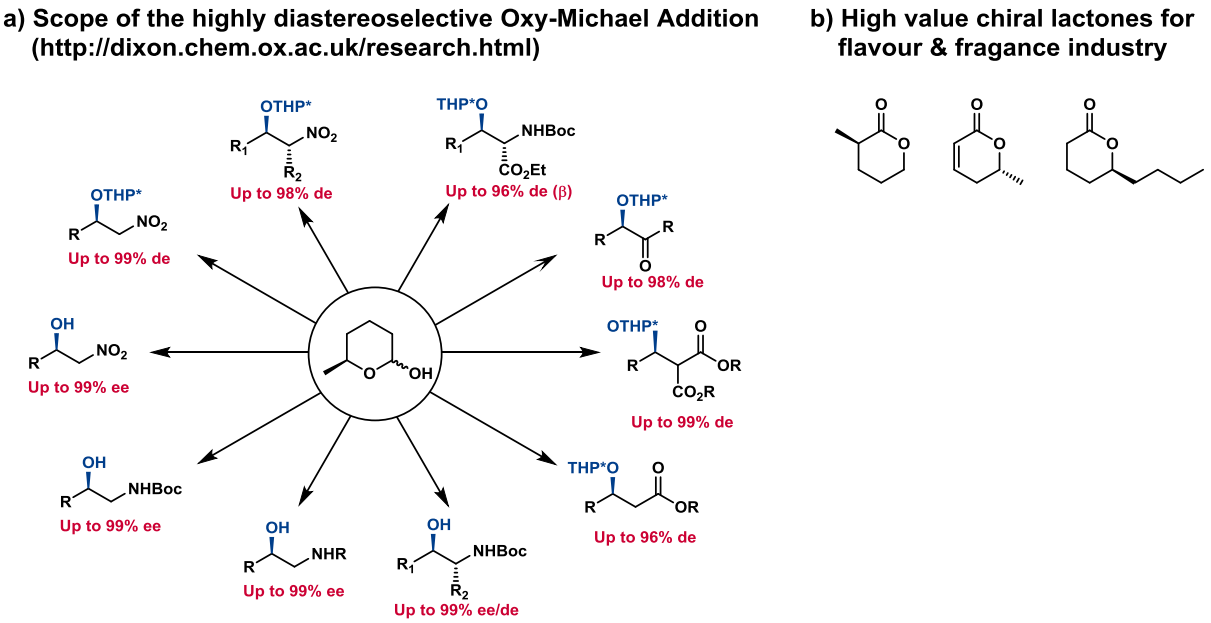

Figure 1. Enantiomerically pure lactols and lactones are important in synthesis and fragrance industry.

2. Aminocatalytic conjugate additions with very low catalyst loadings

This project has extensively studied all the equilibria involved in the reactions of aminocatalysts and precatalyst with nucleophiles. These equilibria are quite similar to the ones involved in aminocatalytic reactions by iminium activation modes. Thanks to the effort made in characterising the different species involved in the equilibria, as well as the parameters affecting their kinetics, we have developed a new technique to run these reactions with very low catalyst loadings.

Usually, iminium activated organocatalytic reactions are run with 10 to 20 mol% of catalyst. This has been identified as one of the major drawbacks of this technology and it is probably one of the reasons why it has not been implemented generally in industry. In addition, these reactions are usually highly irreproducible.

We have identified that the irreproducibility observed in this kind of reactions is mainly due to the presence of unknown and unmeasurable amounts of acid contained in one of the reagents, the aldehyde. In order to solve this problem, we have used a totally innovative strategy, which involves the use of the distribution of catalytic intermediates as the parameter that correlates with the overall rate of the reaction.

This new strategy allow us to build a map to homogenise the conditions starting from totally diverse aldehydes to obtain the same result, therefore solving the irreproducibility problems. In addition, this method is not sensitive to the catalyst loading and allows to run the reaction with a very low catalyst loading. In Figure 2 it is shown how we can use 0.1 mol% of catalyst to perform reactions that previously required 10–20 mol%.

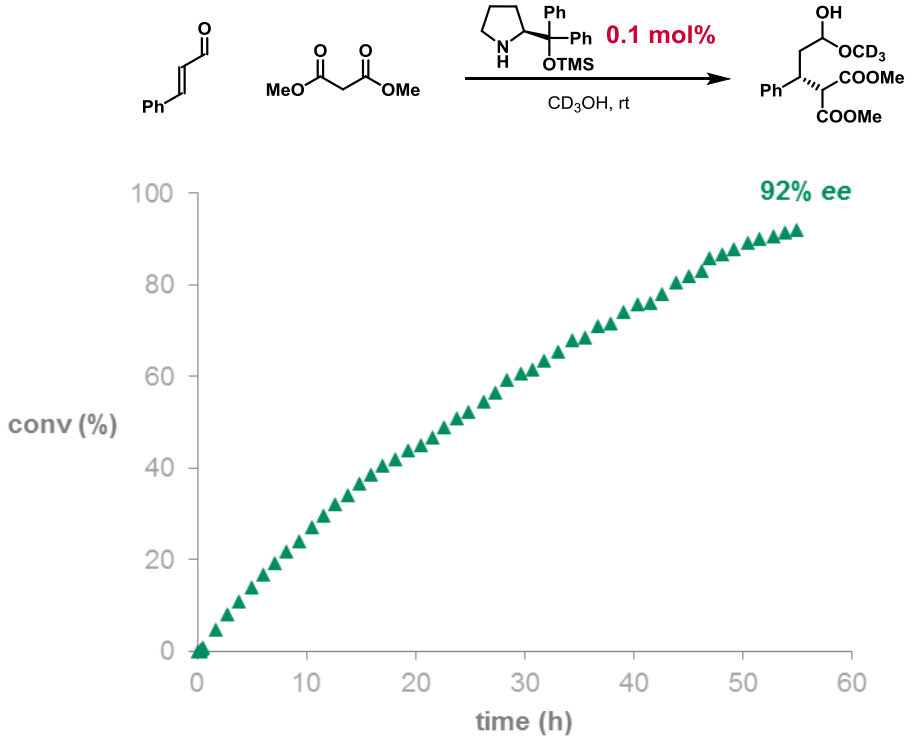

Figure 2. The reaction is completed with just 0.1 mol% of aminocatalyst in less than 60 h.